Persistence of Impaired PRL Responses to Sulpiride in Patients with PRL Secreting Pituitary Adenomas after Successful Hypophysectomy

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HANEw, K., SASAKI, A., SATO, S., KASAI, M., MURATA, K., SHIMIZU, Y., MURAKAMI, O. and YOSHINAGA, K. Persistence of Impaired PRL Responses to Sulpiride in Patients with PRL Secreting Pituitary Adenomas after Successful Hypophysectomy. Tohoku J. exp. Med., 1983, 140 (3), 225-233 — TRH, arginine, L-dopa, and sulpiride tests for PRL secretion were carried out in 18 control subjects and 20 patients with pituitary PRL-secreting adenomas before and after hypophysectomy. After the hypophysectomy PRL levels fell to normal ranges in 9 cases (categorized as Group I), and remained high in 11 other cases (categorized as Group II). After the operation, there were no alterations of PRL responsiveness to TRH, arginine, or to L-dopa in terms of percent change from the basal value, in either Group I or Group II. No significant differences were found in PRL responses to the above three agents between operated Group I patients and normal subjects even when expressed in absolute values. On the other hand, the PRL responses to sulpiride in both Groups I and II improved markedly after the hypophysectomy, but the absolute response in operated Group I patients was still lower than that in normal subjects. The mean PRL value in operated Group I (mean±s.e., 13.2±0.8 ng/ml, n=9) was significantly (p<0.01) higher than in normal subjects (5.1±0.4 ng/ml, n=18). It is concluded 1) that even in hypophysectomized normoprolactinemic patients the circulating PRL may originate mainly from the residual tumor cells, and 2) that the sulpiride test is useful to detect the abnormalities of hypothalamo-pituitary axis in operated patients with PRL-secreting adenomas, whereas TRH, arginine, and L-dopa tests are less useful for such purposes. — PRL-secreting tumors; sulpiride; TRH; L-dopa; dopaminergic abnormality

Recently, patients with prolactin-secreting pituitary adenoma (PRL-noma) have been widely treated by transsphenoidal hypophysectomy (Hardy 1973). The PRL levels of such patients are, however, not always suppressed to normal ranges even after hypophysectomy (Jaquet et al. 1978; Tindall et al. 1978; Barbarino et al. 1979; Murray et al. 1979; Casper et al. 1980; Schlechte and Sherman 1981).

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PRL-noma usually shows reduced or blunted responsiveness of plasma PRL to several agents (Barbarino et al. 1978; Jeske 1979; Cowden et al. 1979; Tucker et al. 1980). Therefore, if the pituitary tumor was removed completely, the recovery of normal lactotrophs from the tumor compression and of PRL responsiveness to exogenous stimuli would be expected. Although there are several reports regarding the changes of responsiveness after hypophysectomy, the results are not always consistent (Barbarino et al. 1979; Murray et al. 1979; Tucker et al. 1980; Schlechte and Sherman 1981).

In this study, we divided the PRL-noma patients into two groups according to the PRL levels obtained after hypophysectomy, namely normoprolactinemic group and hyperprolactinemic one, and evaluated the responsiveness to TRH, arginine, L-dopa, or to sulpiride before and after hypophysectomy.

**Materials and Methods**

*Subjects.* Twenty patients with PRL-secreting adenoma (PRL-noma), 5 males and 15 females, aged 18–55 years, were involved in this study. The diagnosis of PRL-noma was made radiologically (CT-scan, tomography and plain X-ray of sella turcica), and by means of histological studies on the specimens of pituitary surgery, and/or from PRL assays (Table 1). Sixteen cases received transsphenoidal hypophysectomy, and the remaining 4 were operated by transfrontal approach. Even after the hypophysectomy, reserves of other pituitary hormones except PRL were remained normal. None of the subject had been taking any medications throughout the study. For comparison of PRL responsiveness to the above agents, 18 normal healthy subjects, 9 males and 9 females, aged 18–22 years, were studied as a control.

*Procedures.* TRH (500 µg, i.v., Tanabe, Osaka), arginine (10% L-arginine HCl, 0.5 g/kg b.w., infused i.v. for 30 min, Morishita, Osaka), L-dopa (500 mg, p.o., Sankyo, Tokyo), and sulpiride (100 mg, i.m., Delagrange, Paris, France) were administered respectively before the operation and within 2 to 6 months after the hypophysectomy. Details were reported previously (Hanew et al. 1982). The procedures were started between 8 and 9 o’clock in the morning after an overnight fast. Blood samples obtained were centrifuged at 4°C and kept frozen at −27°C until assayed. Plasma PRL values were measured in duplicate with commercial RIA kits as reported elsewhere (Hanew et al. 1980a). Sellar volume was calculated according to the methods of Di Chiro and Nelson (1962). All tests of statistical significance were performed using Student’s paired t test. A p value less than 0.05 was considered statistically significant.

**Results**

*Basal plasma PRL levels before and after hypophysectomy*

Before hypophysectomy the basal plasma PRL in twenty cases of PRL-noma ranged from 23 to 2,408 ng/ml (mean±s.e. 364.2±122.5 ng/ml). After hypophysectomy PRL value decreased to 28.2% of the pretreatment value (102.6±50.2 ng/ml, ranged 9.3 to 956 ng/ml) (Table 1). The PRL value was normalized (below 18 ng/ml) in 9 cases (Nos. 1–9, categorized as Group I) and not normalized in the other 11 cases (Nos. 10–20, Group II) (Table 1, Fig. 1). The mean PRL values in Groups I and II were 13.2±0.8 ng/ml (range 9.3–16 ng/ml) and 175.7±86.7 ng/ml (range 18.8–956 ng/ml), respectively. The former value, however,
TABLE 1. Clinical and laboratory data in 20 patients with PRL-noma

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<th>Surgical approach‡</th>
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* PRL-secreting microadenoma with the bulging of sellar floor.
† chr, chromophobic; acid, acidophilic; N.D., not determined.
‡ F, transfrontal; S, transphenoidal.

Fig. 1. Basal plasma PRL levels in 20 patients with PRL-noma before and after hypophysectomy. Shaded area represents the normal ranges.
was significantly \( (p<0.001) \) higher than that of 18 normal controls \( (5.1\pm0.4 \text{ ng/ml, } n=18) \).

**Plasma PRL responses to TRH in 19 patients with PRL-noma**

Before hypophysectomy, plasma PRL in 19 patients with PRL-noma (total group) showed 186.3\( \pm \)23.6\% increase from the basal value 30 min after TRH injection. Plasma PRL responses to TRH after hypophysectomy was quite similar to that before the operation \( (208.8\pm31.0\% \text{ increase at 30 min, } p>0.05) \) (Fig. 2 left). Again there was no difference in the mean peak value between pre- \( (202.2\pm29.4\%) \) and post-operation \( (217.8\pm30.1\% \text{ } p>0.05) \). Moreover, the PRL responses to TRH in Group I or II were quite similar throughout the study (Fig. 2 center and right). The PRL responses in Group 1, however, were greater than in Group II either before or after the hypophysectomy (both \( p<0.005 \)).

In contrast, normal subjects showed significantly greater PRL responses to TRH \( (379.0\pm51.5\%, \text{ } n=10) \) than the Group II patients before or after the operation. There were, however, no significant differences between the maximal PRL responses in normal subjects and Group I patients after hypophysectomy either in percent changes \( (379.0\pm51.5 \text{ vs. } 294.1\pm57.2\%) \) or in absolute values \( (35.0\pm3.5 \text{ vs. } 41.0\pm9.5 \text{ ng/ml}) \).

**Plasma PRL responses to arginine in 10 patients with PRL-noma**

After arginine infusion plasma PRL in 10 patients showed only a subtle increase, and there were no differences between the peak values before \( (127.3\pm11.8\%) \) and after hypophysectomy \( (130.7\pm16.8\%) \) (Fig. 3, left). Again, no significant changes in the responsiveness were observed in Group I or II even after the operation (Fig. 3, center and right). Before the hypophysectomy the

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**Fig. 2.** Plasma PRL responses to TRH in 19 patients with PRL-noma before and after hypophysectomy. Details are explained in the text. ●○●, untreated; ○○○, treated.
response in Group I was significantly greater than in Group II \( (p<0.05) \). Six normal subjects showed greater PRL responses to arginine \( (260.0\pm52.4\%, \ n=6) \) than total group \( (p<0.02 \) before treatment and \( p<0.05 \) after treatment). However, the maximal PRL responses in normal subjects were not significantly different from those in operated Group I patients either in terms of percent changes \( (260.0\pm52.4 \) vs. \( 158.6\pm19.5 \)) or in absolute values \( (14.9\pm1.9 \) vs. \( 18.7\pm5.1 \) ng/ml).

Fig. 3. Plasma PRL responses to arginine in 10 patients with PRL-noma before and after hypophysectomy. ●—●, untreated; ○---○, treated.

Fig. 4. Plasma PRL responses to L-dopa in 11 patients with PRL-noma before and after hypophysectomy. ●—●, untreated; ○---○, treated.
Plasma PRL responses to L-dopa in 11 patients with PRL-noma

As shown in Fig. 4, PRL responses to L-dopa in 11 patients were not changed after the surgery. The maximal PRL decreases were 37.9±7.0% of the basal value before and 41.3±4.3% after the operation (p>0.05, Fig. 4, left). The PRL responses in Group I were higher than in Group II regardless of the treatment (p<0.05). There were no significant differences in the maximal PRL responses between operated Group I and ten normal subjects either in percent changes (35.1±4.0 vs. 33.7±2.9%) or in absolute values (4.0±0.9 vs. 2.9±0.3 ng/ml). Moreover, compared to normal subjects, the maximal percent decreases in total group were not statistically different, although the decreases were significantly less in Group II regardless of the treatment.

Plasma PRL responses to sulpiride in 14 patients with PRL-noma

Fourteen untreated patients with PRL-noma showed a slight increase in PRL secretion to the administration of sulpiride. After the hypophysectomy they responded to the same stimulus with a marked PRL increase (Fig. 5, left). The PRL response at 15 min was significantly (p<0.05) higher in operated group (189.7±29.4%) than in untreated (123.6±9.0%). Similar improvement of the responsiveness was observed either in Group I or Group II, while the response in the former was larger than that in the latter. However, the PRL responses in these PRL-noma patients were significantly (p<0.001) lower than those in 18 normal subjects (1,684.0±168.4%).

Fig. 5. Plasma PRL responses to sulpiride after hypophysectomy. -.-, untreated; o---o, treated.
DISCUSSION

In this study we found no alterations of PRL responsiveness to TRH, arginine, or L-dopa in terms of percent changes from the basal value in patients with PRL-secreting adenoma after the hypophysectomy. In addition, there were no significant differences in PRL responsiveness to the above three agents between the surgically normalized group and normal subjects either in percent changes or in absolute values.

In contrast, the PRL responsiveness to sulpiride improved markedly after the hypophysectomy, whereas the response in Group I patients was still lower than that in normal subjects. The normalization of PRL-responses to TRH after successful hypophysectomy confirms the previous reports (Barbarino et al. 1979; Tucker et al. 1980; Schlechte and Sherman 1981), although these authors could not observe the distinct responses before the surgery.

A sulpiride test was employed in this study to detect the dopaminergic abnormalities in the hypothalamus and pituitary gland, since PRL is released as a result of blockade of the inhibitory dopaminergic mechanism (Banakis and Stefan 1977; Crosignani et al. 1977; MacLeod and Robyn 1977; Quigley et al. 1979; Hanew et al. 1980b).

The improvement of PRL responsiveness to sulpiride after the hypophysectomy in normo- and hyper-prolactinemia indicates the possibility that some alterations of dopaminergic influences on the hypothalamus and pituitary have occurred concomitantly with PRL decreases regardless of the PRL levels. However, as the PRL responsiveness to sulpiride did not normalize, the following possibilities may be considered: 1) Pituitary tumor has been removed completely, but the hypothalamic dopaminergic abnormalities persist. 2) Hypothalamic dopaminergic influences are normal, but residual tumor tissues are still secreting PRL. 3) Hypothalamic abnormalities and residual tumors coexist.

In operated Group I patients, the mean basal PRL values were significantly higher than in normal subjects. It can be assumed that the function of normal lactotrophic cells around the tumor tissue is suppressed by the compression as well as by the short- and/or ultra short-loop feedback effects induced by elevated PRL levels (Hökfelt and Fuxe 1972; Meites et al. 1972; Gudelsky and Porter 1980; Scanlon et al. 1981; Schlechte and Sherman 1981). Therefore, PRL levels should be much lower than those in normal subjects if PRL-noma was removed completely. Accordingly, the high-normal PRL levels in normoprolactinemic patients after the hypophysectomy indicate the presence of residual tumors, and the PRL in systemic circulation may originate mainly from the adenoma cells. The inadequate PRL responses in PRL-noma seen after the hypophysectomy may be due to the reduced sensitivities of adenoma cells to the blocking effect of sulpiride on an inhibitory dopaminergic mechanism. We cannot, however, rule out the possibility that such inadequate responses depend more or less upon the hypothalamic dopaminergic abnormalities (Fine and Frohman 1978).

The reason why the PRL responses in Group I are more marked than in Group
II even before the hypophysectomy is not clear. A possible mechanism we can speculate from these results is that the more responsive types of PRL-noma to exogenous stimuli are apt to be normalized in their PRL levels following hypophysectomy.

In conclusion, the sulpiride test is useful to examine the presence of residual pituitary tumors and of hypothalamic dopaminergic derangement, whereas TRH, arginine, and L-dopa tests are less useful for such purposes. Namely, when PRL responses to sulpiride after hypophysectomy were completely reverted to normal, it is very plausible to conclude that pituitary adenoma was entirely removed and hypothalamic dopaminergic mechanisms were operating normally.

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References


