Evidence for Endogenous Dopaminergic Control of GH Release in Man

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HANEW, K., SASAKI, A. and YOSHINAGA, K. Evidence for Endogenous Dopaminergic Control of GH Release in Man. Tohoku J. exp. Med., 1981, 135 (1), 103–108 — In order to determine whether or not there is a tonic dopamine (DA) control of GH release, the effect of an anti-dopaminergic agent, sulpiride, on GH secretion was studied in 12 normal subjects. After the administration of sulpiride, serum concentrations of sulpiride reached a peak value (1.93±0.1 µg/ml, mean±S.E.M., n=6) at 15 min and then showed a gradual decrease. Concomitantly, mean plasma prolactin (PRL) showed a rapid elevation, with a peak value of 161.9±11.5 ng/ml at 30 min, followed by a gradual decrease. Even at 180 min after sulpiride injection, the plasma PRL was still 9 times higher than the initial level (p<0.005). Within 90 min after the injection, 12 subjects showed a minimal but significant decrease in GH (from 0.78±0.17 to 0.32±0.03 ng/ml, p<0.02). After another 90 min, the plasma GH level increased and the mean peak value (8.1±2.7 ng/ml) at 180 min was significantly higher than the initial value (p<0.02). From these observations, it was suggested that sulpiride inhibited the endogenous DA activity over 180 min, and that the GH decrease within 90 min was due to a suppression of endogenous DA activity. Factors other than DA, however, might be considered for the GH increase after 90 min. ——— dopamine; GH; prolactin; sulpiride

It is well known that dopaminergic agonists, e.g. L-dopa, apomorphine, pirebedil and CB-154, have stimulatory effects on GH secretion in man (Eddy et al. 1971; Lal et al. 1972; Camanni et al. 1975; Orsetti et al. 1978). In addition, it has been reported that dopamine (DA)-antagonists, e.g. pimozide and sulpiride, can inhibit the GH release induced by DA-agonists (Liuzzi et al. 1976; Lal et al. 1977; Mori et al. 1977). These findings suggest a role for DA in the release of GH. Effects produced by pharmacological doses of DA-agonists, however, do not necessarily imply that endogenous DA has a physiological role in the control of GH secretion. To test whether this is in fact the case, we examined the effect of a DA-antagonist, sulpiride (Restelli et al. 1975; MacLeod and Robyn 1977). If there is a tonic DA control of GH release, sulpiride would be expected to block it with resultant changes in plasma GH.

Received for publication, December 22, 1980.

This work was partly supported by the Research Grant for Specific Disease of the Japanese Ministry of Health and Welfare and a Research Grant from the Japanese Ministry of Education, Science, and Culture.
MATERIALS AND METHODS

Twelve volunteer subjects (19–22 years old), eight men (Nos. 1–4, 7, 8, 11, 12) and four women (Nos. 5, 6, 9, 10), with apparently normal endocrine function were studied. Of the four women, two (Nos. 5, 9) were in the follicular phase and two (Nos. 6, 10) were in the luteal phase of their menstrual cycle. The body weight of all subjects was within normal ranges. At 08:00 h after an overnight fast, an i.v. catheter was inserted in an antecubital vein for blood sampling and kept open with normal saline. After basal plasma samples were taken, 100 mg sulpiride (Delagrange; Paris, France) was injected i.m. (below 2.2 mg/kg b.wt) and blood samples were drawn at subsequent intervals for hormone and sulpiride determinations. None of the subjects complained of specific symptoms while on sulpiride treatment.

Plasma GH and PRL levels were determined according to methods previously reported (Hanew et al. 1980a). The minimal sensitivity of the GH assay system was 0.2 ng/ml (Rodbard 1978). Serum concentrations of sulpiride were determined by Fujisawa Pharmaceutical Co. (Osaka, Japan) using the spectropho-fluorometric method as follows: Two ml of 1 M glycine buffer solution were added to 1 ml of serum in a 30 ml glass tube. Fifteen ml of chloroform were then added. The tubes were shaken for 10 min and centrifuged for 10 min at 3,000 rpm. Fifteen ml of the chloroform solution was transferred to a small tube containing 3 ml of 1 N sodium hydroxide (NaOH). The tubes were shaken for 10 min and then centrifuged for 10 min at 3,000 rpm. The NaOH solution was transferred to another tube and 2 ml of 4 N perchloric acid was added. The fluorescence of the solution was measured and results read on a standard curve. Fluorescence measurements were made with an Aminco-Bowman Spectropho-fluorometer. Maximal fluorescence was obtained with an activating wavelength of 250 nm, whereas emission was measured at 390 nm. The minimal detectable level of sulpiride in this assay system was 0.05 µg/ml. Analysis of variance and Student's two tailed t test were used for data evaluation, and the variance of the mean was expressed as s.e.m.

RESULTS

Twelve normal subjects received an intramuscular injection of 100 mg sulpiride and the serum sulpiride levels were determined in 6 cases (Nos. 1, 4, 7, 8, 11, 12). After the injection, all six cases showed dramatic elevations and gradual declines of the serum sulpiride levels (Fig. 1). The mean peak value (1.93±0.1 µg/ml) was seen at 15 min after the injection and the mean half life calculated from the slope after 120 min was 3.4±0.3 hr.

Concordantly with the elevation of the serum sulpiride levels, plasma PRL levels in the 12 subjects showed a rapid increase followed by a gradual decrease (Fig. 1). The mean peak value (167.3±12.7 ng/ml) was observed at 30 min after the injection, and from 15 to 240 min mean PRL values were significantly higher (p<0.005) than the mean initial value (8.3±0.8 ng/ml).

As shown in Fig. 1, the 12 subjects showed distinct decreases and subsequent increases of plasma GH. Although, according to analysis of variance, the mean GH decrease within 90 min did not reach statistical significance, the mean of each minimal value (0.32±0.03 ng/ml) was significantly lower than the initial value (0.78±0.17 ng/ml; p<0.02). After 90 min the mean plasma GH level showed an elevation and reached a peak value at 180 min which was significantly higher than that of the initial value (p<0.005). The mean of each maximum value (8.1±2.7 mg/ml) was also significantly higher than the initial value (p<0.02).
DISCUSSION

The present study demonstrated that intramuscular administration of sulpiride caused monophasic increases in serum sulpiride and plasma PRL as well as biphasic responses in plasma GH in the 12 normal subjects studied.

It is widely accepted that DA is one of the major regulators of PRL secretion, and i.v. administration of physiological concentrations of DA, such as seen in the pituitary stalk plasma, is capable of inhibiting pituitary PRL secretion in normal rats (Gibbs and Neill 1978; Gudelsky and Porter 1979). In this study, the mean PRL value from 15 to 240 min after the sulpiride injection was significantly higher than the mean initial value. There were no significant differences between the mean PRL values at 180 min (74.1±9.7 ng/ml) and 240 min (59.7±10.7 ng/ml). The metabolic half life of plasma PRL is reported to be about 53 min (Sievertsen 1980). If sulpiride induced DA inhibition, and the stimulated PRL release were not maintained, PRL value at 240 min should be below 50% of the value at 180 min. Accordingly, it is suggested that sulpiride has significantly blocked the endogenous DA activity over 180 min. Therefore, it is probable that the initial GH decrease within 90 min was caused by the interruption of the endogenous DA activity, and that sulpiride might act at the level of hypothalamic DA neurons (Martin 1976; Müller et al. 1977).

The i.v. infusion of DA, which does not cross the blood brain barrier, induces
GH increase in normal subjects (Burrow et al. 1977; Langer et al. 1978; Woolf et al. 1979), while DA administration to in vitro pituitaries from both normal and acromegalic subjects reversely causes GH decreases (Goodyer et al. 1978; Peillon et al. 1979). These findings suggest a direct action of DA on pituitary somatotropes in man, although such contradictory responses to DA are still open to discussion. From these observations, direct effects of sulpiride on somatotropes should be taken into consideration. The fact that sulpiride can stimulate PRL release by a direct action on mammotropes might lend support for the above explanation (MacLeod and Robyn 1977; Hanew et al. 1980b).

Concerning the GH increase after 90 min, however, it is not plausible that an endogenous dopaminergic pathway is involved in this increase because the sulpiride was already effectively blocking the DA-activity with resultant PRL release as long as 4 hr. Rather, it is assumed that the GH increases were evoked by an increased endogenous GH-RF (GH-releasing factor), decreased endogenous GH-IH (GH-release inhibiting hormone), or rebound release of stored GH from somatotropes as a result of inhibited GH release (Martin 1976; Müller et al. 1977). It has been reported that psychological and physical stress can enhance GH release (usually GH levels are over 5 ng/ml) in man and other primates (Greenwood and Landon 1966; Brown et al. 1971; Brown and Reichlin, 1972). In this study, however, the initial GH decrease could not be due to a fall from an initially elevated level, because the initial GH levels were rather in low normal ranges (from 0.3 to 2.1 ng/ml). To clarify these biphasic phenomena, further study would be required. Our data are at variance with the earlier observation that intramuscular injection of sulpiride (4 mg/kg b.wt) did not affect GH secretion in 5 normal subjects (L’Hermite et al. 1978). At present, we have no explanation for these discrepancies.

In conclusion, endogenous DA might have a tonic stimulatory role on GH secretion in man, although GH secretion is physiologically regulated by multiple factors.

Acknowledgment

We are especially grateful to Dr. Edward G. Rennels for his invaluable criticism on this manuscript. We thank to Mr. Stephen Price and Mr. John R. McGill for their kind cooperation. We also appreciate the expert measurement of serum sulpiride levels by Mr. T. Kitaura and Mr. T. Sawada in Fujisawa Pharmaceutical Co.

References
