EFFECTS OF L-DOPA ON PROLACTIN SECRETION IN HUMANS

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ALTHOUGH prolactin was identified as a constituent of animal pituitaries more than 40 years ago, it is only within the last few years that the regulation of this hormone has come under intensive investigation, largely as a result of the development of sensitive radioimmunoassays in several species. Even more recent has been the demonstration of a human prolactin, separate from growth hormone, which circulates in human blood (FRANTZ and KLEINBERG, 1970). The isolation of this hormone from monkey and human pituitaries (LEWIS *et al.*, 1971; HWANG *et al.*, 1972) has permitted the development of homologous human radioimmunoassays (HWANG *et al.*, 1971; SINHA *et al.*, 1973). Heterologous radioimmunoassay systems have also been developed by which the human hormone can be studied (JACOBS *et al.*, 1972; L'HERMITE *et al.*, 1972). Many physiologic and pharmacologic factors have been found to affect plasma prolactin in humans, including nursing or breast stimulation, sleep, stress, pregnancy, estrogens, sexual intercourse, neuroleptic drugs, thyrotropin releasing hormone (TRH), and L-dopa; these and other factors in the regulation of human prolactin have recently been reviewed (FRANTZ, 1973).

The studies to be presented here concern some effects of L-dopa on prolactin in humans. A prominent role of dopamine in the regulation of prolactin had been indicated by animal experiments, and we as well as others had found that L-dopa given orally to humans could produce transient depression of both pathologically elevated and normal plasma prolactin concentrations (KLEINBERG *et al.*, 1971; MALARKEY *et al.*, 1971; FRIESEN *et al.*, 1972; FRANTZ *et al.*, 1973). We had also found that L-dopa pre-treatment could inhibit the rise in prolactin produced by chlorpromasine (KLEINBERG *et al.*, 1971), a drug known to act at the hypothalamic level by blocking release of prolactin inhibiting factor (PIF). The present studies explore the effects of L-dopa on TRH-stimulated prolactin release, as well as its use in conjunction with the L-dopa decarboxylase inhibitor L-alpha-methyldopa hydrasine (MK-486).

MATERIALS AND METHODS

Subjects were healthy normal volunteers aged 21–27, studied in the morning after an overnight fast. Blood samples were collected through an antecubital vein at the start of the experiment. L-dopa and MK-486 were administered orally. TRH, either 100 μg or 500 μg, was given intravenously over 30 sec. Prolactin was measured by homologous human radioimmunoassay as previously described (FRANTZ *et al.*, 1972). Growth hormone was also measured by radioimmunoassay (FRANTZ and RABKIN, 1964).

RESULTS

Response to TRH alone and with L-dopa pre-treatment

TRH given alone to 7 normal women and 7 normal men caused the expected acute rises in plasma prolactin shown by the solid lines in Figs. 1a and 1b. These results are

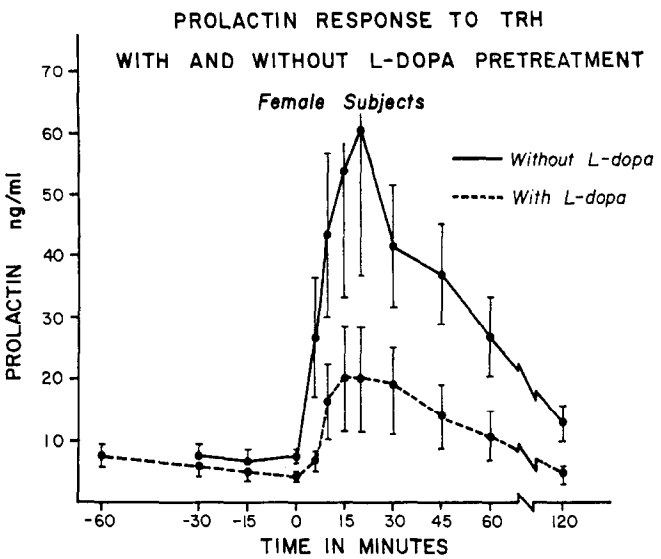

FIG. 1a

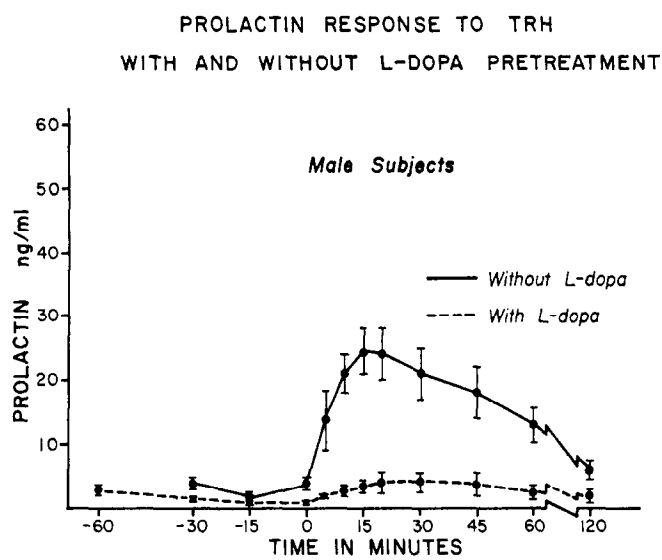

FIG. 1b

FIG. 1.—Prolactin response to intravenous TRH at 0 min without and with pretreatment with L-dopa. 1a (top): Response in 7 normal women. 1b (bottom): Response in 7 normal men. Vertical bars denote standard error of the mean.

similar to what has been reported by others (BOWERS *et al.*, 1971; JACOBS *et al.*, 1971). Women as a group were more responsive than men to TRH; a greater responsiveness in women has also been noted to other kinds of prolactin-releasing stimuli (NOEL *et al.*, 1972). Several days after the studies with TRH alone, the same subjects were given the same dose of TRH but were pretreated with 500 mg of L-dopa an hour beforehand; 11 of the 14 subjects received an additional 250 mg of L-dopa 30 min

before the TRH. The responses are shown in the dotted lines of Figs. 1a and 1b. Except for one woman whose TRH response was unchanged by L-dopa, a clear suppressive effect was evident in all subjects. Mean prolactins after L-dopa were significantly lower at all time points from +10 to +60 min in the group of women as a whole ($P < 0{\cdot}02$), as well as in the group of men ($P < 0{\cdot}005$). No difference in peak prolactin response in either sex was evident after 100 μg of TRH as compared with 500 μg, either with or without L-dopa pre-treatment. Those who received 750 mg of L-dopa did not show more or less suppression than those who received 500 mg.

L-dopa compared with L-dopa plus MK-486 in normals

The effect of a single dose of 500 mg of L-dopa was compared with that of 100 mg of L-dopa given together with 50 mg of MK-486 on a subsequent occasion in each of 6 normal subjects (3 men, 3 women). On a third occasion a placebo was administered and the subjects were followed as before. The effects on prolactin are shown in Fig. 2. A pronounced and statistically significant drop in prolactin, maximal at 2 hr, is evident in subjects receiving either L-dopa alone or L-dopa with inhibitor. An apparent rebound to greater than normal levels occurs at 6 hr, though the differences at this point are not statistically significant because of wide scatter. There were no statistical differences between the prolactin responses to L-dopa alone and to L-dopa with MK-486. Growth hormone stimulation, previously noted by others after L-dopa administration (Boyd *et al.*, 1970) occurred to an equal degree with both L-dopa regimens (Fig. 3). Mean plasma L-dopa concentrations* showed no statistical difference at any time from 20 min to 24 hr when the two regimens were compared.

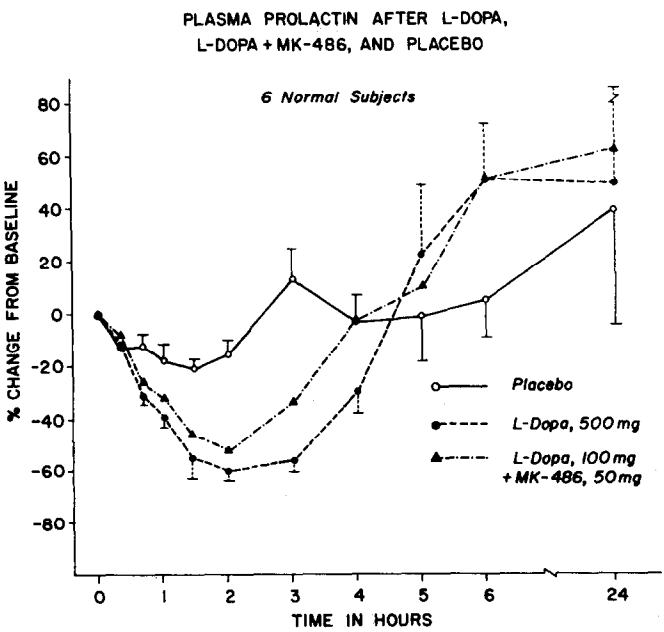

FIG. 2.—Plasma prolactin after L-dopa, 500 mg; after L-dopa, 100 mg, plus MK-486, 50 mg; and after placebo. All drugs were given orally at 0 time on separate occasions several days apart. Vertical bars denote standard error of the mean.

* Performed by Dr. George Breault of the Merck Sharp & Dohme Research Laboratories.

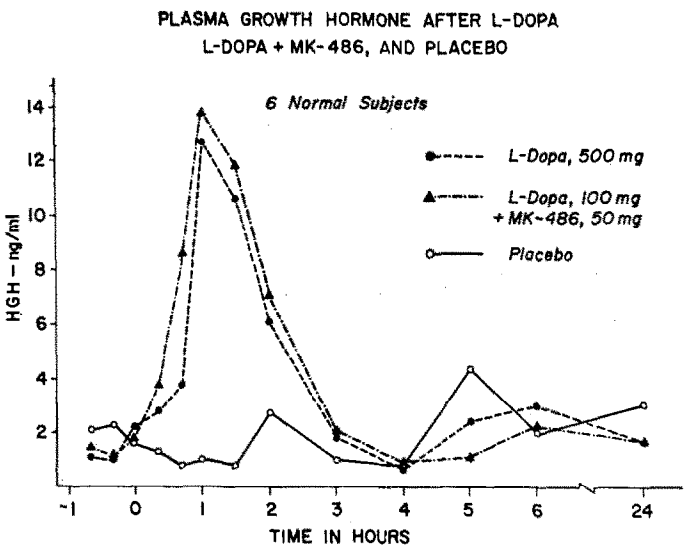

FIG. 3.—Plasma growth hormone concentrations in the same samples as those depicted in Fig. 2.

DISCUSSION

The inhibitory effect of L-dopa on prolactin has been assumed to be mediated via stimulation of hypothalamic PIF, largely on the basis of work by KAMBERI *et al.* (1970; 1971) showing that dopamine infused into the third ventricle raised PIF in portal blood and decreased prolactin release, whereas direct infusions of dopamine into the anterior pituitary did not affect prolactin levels in peripheral blood. Three other groups have obtained evidence for a direct inhibitory action of dopamine or other catecholamines on pituitary prolactin release in vitro, however, although the doses required have been comparatively large (BIRGE *et al.*, 1970; MACLEOD *et al.* 1970; KOCH *et al.*, 1970). Since TRH is presumed to act directly on the pituitary, the present studies suggest that dopamine may also act at this locus in vivo to antagonise TRH; they are also compatible with the more widely held view, however, that dopamine acts via the hypothalamus; in this case the PIF liberated would presumably be sufficient to overcome the stimulating effect of TRH on the pituitary. A third possibility, namely that TRH may act on the hypothalamus as well as on the pituitary to promote prolactin release, deserves consideration in view of the work of PRANGE *et al.* (1972) and KASTIN *et al.* (1972) showing evidence of extra-pituitary actions of TRH.

The studies with MK-486 demonstrate that this agent may prove useful in conjunction with L-dopa when the latter is used for its effect on the pituitary in promoting growth hormone release or suppressing prolactin. The latter possibility has particular relevance in view of the recent findings by ourselves and others that remission of disease may occur in some individuals with metastatic breast cancer treated chronically with L-dopa (FRANTZ *et al.*, 1973).

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