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THE ROLE OF DOPAMINE IN THE CONTROL OF GONADOTROPIN AND PROLACTIN SECRETION IN THE HUMAN FEMALE.

by

STEPHEN J. JUDD, M.B. B.S., (Adel.), F.R.A.C.P.

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Department of Reproductive Medicine,
University of California, San Diego,
La Jolla, California.

and

Garvan Institute of Medical Research,
St. Vincent's Hospital,
Darlinghurst, New South Wales.

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SUMMARY

This dissertation examines the hypothesis that Dopamine (DA) neurons of the tubero-infundibular system not only control Prolactin secretion from the pituitary gland, but also inhibit the secretion of Luteinising Hormone releasing factor (LRF) from the nerve terminals in the median eminence.

There is evidence to support this contention in the experimental animal. Immuno-histofluorescence studies have demonstrated a conglomeration of both DA and LRF nerve terminals in the lateral pallisade zone of the median eminence (Lofstrom et al., 1976). Electron microscopic study has shown that nerve terminals containing granules of various sizes, presumably both LRF and DA, are closely anatomically related in this region (Kobayashi et al., 1970).

Pharmacological manipulation of brain levels of DA have also supported the concept that DA inhibits LRF secretion. Studies of the turn-over of DA in the lateral pallisade zone, which apparently reflects DA neuron activity, show that DA turn-over is increased when serum LH levels are decreased and vice versa (Fuxe et al., 1969; Fuxe et al., 1969a). Oestrogen treatment of castrated rats causes an increase in DA turn-over which correlates well with the fall of serum LH (Lofstrom et al., 1977).

Administration of DA or DA receptor agonists causes a decrease in episodic LH secretion (Drouva and Gallo, 1976) and a decrease in serum LH (Mueller et al., 1976; Wuttke et al., 1971). In vitro studies with rat pituitary gland incubations have consistently demonstrated that DA has no effect on LH secretion although it actively inhibits PRL release from the pituitary gland. However, LH secretion is

inhibited when DA is incubated with the pituitary left attached to the hypothalamus (Miyachi et al., 1973).

In the human, several studies failed to show any effect of L Dopa on serum LH levels, but a recent careful study did demonstrate a decrease in serum LH with both L Dopa and the DA receptor agonist, bromocriptine (Lachelin et al., 1977). Infusion of DA at a constant rate also caused a decrease in serum LH in normal men and women (Lachelin et al., 1976).

An attempt was made to further study a possible effect of DA on LRF secretion in the human by examining the change in serum LH and FSH, induced by DA, in women with different levels of endogenous LRF secretion. Women studied in the early or mid-follicular phases of the menstrual cycle with DA showed a small but consistent decrease in serum LH but no significant alteration in serum FSH. In contrast, there was a marked decrease in LH and also, to a lesser extent, FSH in women in the pre-ovulatory phase, at a time when endogenous secretion of LRF is believed to be high (3.31.1). Control experiments showed that the effect of DA on LH and FSH secretion could not be reproduced by infusion of saline or noradrenaline (3.33; 3.34).

The LH and FSH responses to DA are also augmented in agonadal women in whom there is a presumed increase in endogenous LRF. Administration of oestrogen, which reduces LRF secretion, impairs the effect of DA on serum LH and FSH (3.36). The LH and FSH response to DA appears to correlate better with basal serum LH reflecting the endogenous level of LRF than the circulating level of oestradiol.

In contrast, the effect of DA on PRL secretion seemed more closely correlated to circulating serum oestradiol.

An attempt was made to exclude a direct effect of DA on the pituitary secretion of LH by studying the LH and FSH responses to exogenous LRF before and during a DA infusion (3.35). These results, however, were not conclusive since it was not possible to exclude an effect on endogenous LRF secretion. In vitro studies using incubated rat hemi-pituitaries (6.32) did not show any effect of DA on the spontaneous or stimulated release of LH (6.31; 6.32).

It is concluded from these studies that DA reduces serum levels of LH and FSH by inhibiting the endogenous release of LRF. It appears that the LH response to DA is a reliable, though indirect, reflection of the rate of endogenous LRF secretion.

In view of this effect of exogenous DA on LRF secretion, it could be postulated that the tubero-infundibular DA neurons exert a similar control, in physiological situations, on the secretion of LRF. If this was so, then blockade of the action of DA on LRF neurons would be expected to lead to an increase in serum LH and FSH. The means by which DA acts on LRF neurons is not established but, on the basis that it was most likely to be through a specific receptor for DA, the acute effect of DA receptor blockade on serum LH and FSH was studied. Since most of the known DA receptor antagonists are either non-specific in their action (e.g. chlorpromazine) or else they cannot be given intravenously (e.g. pimozide), it was decided to investigate the possibility that metoclopramide, an anti-emetic drug which had been shown to cause an increase in serum prolactin

(McNeilly et al., 1974), might be a useful alternative as a DA receptor antagonist.

Initial studies strongly supported the view that metoclopramide (MCP) increased PRL by blocking the action of endogenous DA at the lactotrope receptors. Stimulation of PRL secretion by MCP could be blocked by L Dopa, bromocriptine (4.32) and DA (4.33) in normal men and women. In vitro studies excluded a direct stimulation of PRL secretion by MCP (6.33) and indicated that there was mutual antagonism between DA and MCP for lactotrope receptors.

Despite this effect on serum PRL, MCP had no significant effect on serum LH and FSH in either the 0.5 mg (4.34.2) or 2.5 mg dose (4.34.1). Hence, it was not possible to confirm that DA neurons exert a tonic inhibitory control of LRF secretion in the normal human; however, neither was it possible to exclude this. The possibility is discussed that DA may inhibit LRF secretion by a mechanism which does not involve specific receptors, or if it does then these receptors may be less sensitive to the effect of MCP than is the lactotrope receptor.

An intriguing speculation which is raised by the possibility of dopaminergic control of LRF secretion, is that certain disorders in the human associated with chronic anovulation, may be mediated by an over-activity of the tubero-infundibular neurons suppressing LRF release. One such condition, chronic anovulation associated with hyperprolactinaemia, has been investigated because animal studies have previously concluded that hyperprolactinaemia, itself, may induce excessive dopaminergic activity in the hypothalamus.

Ten women with microadenomas causing hyperprolactinaemia, were studied with infusions of DA and injections of MCP. DA infusion suppressed serum LH in hyperprolactinaemic women, but to a significantly smaller degree than normal women in the early follicular phase of the cycle (5.31). This was interpreted as being consistent with a decreased secretion of endogenous LRF. However, the possibility that this might result from over-activity of DA neurons could not be confirmed because there was again no LH or FSH response to MCP, at the dose used (5.32).

Although the PRL response to MCP is significantly reduced in hyperprolactinaemic women, the rapid PRL response to DA indicates that the lactotrope receptors are functionally active. This raises the possibility that the pathogenesis of hyperprolactinaemic chronic anovulation may be related to a failure of the short loop feed-back control of excessive PRL release at the pituitary level, while excessive DA activity in the hypothalamus inhibits LRF secretion. Possible disturbances in dopaminergic neurotransmission in other human anovulatory diseases are discussed.