Methylprednisolone retained 70% of PGDH activity in endotoxemic rat lung. Order No. 74-12,319, 117 pages.

EFFECTS OF CENTRAL ACTING DRUGS AND ERGOT DERIVATIVES ON PROLACTIN AND GROWTH HORMONE SECRETION, ON GROWTH OF PITUITARY AND MAMMARY TUMORS AND ON REPRODUCTION IN OLD RATS

QUADRI, Syed Kaleemullah, Ph.D.
Michigan State University, 1974

1. A single intraperitoneal injection of the ergot derivatives, ergocryptine, or LSD (lysergic acid diethylamide), significantly decreased serum prolactin levels in female rats and blocked the rise in prolactin that normally occurs in control rats on the afternoon of proestrus. A single dose of ergocryptine remained effective for at least 24 hours after it was administered. Ergocryptine was not able to block the increase in prolactin secretion induced by perphenazine, which exerts its effects on the hypothalamus. The primary action of ergocryptine appears to be directly on the pituitary gland.

2. A single intraperitoneal injection of 1, 8 or 12 mg pyrogallol per 100 g body weight caused a significant reduction in serum prolactin levels in female rats. Pyrogallol inhibits degradation of catecholamines, and an increase in catecholamines results in reduced prolactin secretion.

3. A single intraperitoneal injection of sodium pentobarbital produced an initial rise followed by a fall in plasma growth hormone (GH). Ether anesthesia consistently reduced plasma GH levels. Contrary to their inhibitory effects on GH secretion in rats, stresses of various kinds stimulate GH release in man and other species.

4. Daily injections of epinephrine, l-dopa or iproniazid for 25 days into 20 to 23 month old constant estrous Sprague-Dawley rats initiated regular estrous cycles in most rats. On termination of treatment, a few rats continued to cycle but the majority returned to a state of constant estrous or went into a prolonged diestrus. It was concluded that all three drugs restored regular cycling by correcting a catecholamine deficiency in the hypothalamus, thereby increasing LH and FSH and decreasing release of prolactin.

5. Inbred female Wistar-Furth rats were transplanted with the mammosomatotropic pituitary tumor, MtT. W15. About 6 weeks after transplantation, weekly measurements were made of plasma GH, serum prolactin, tumor size and body weights. A highly significant and positive correlation was found between tumor size and prolactin and GH levels, and between tumor size and body weight. Age of tumor was not always related to the secretory activity or size of the tumor.

6. Daily treatment of rats carrying pituitary tumor transplants with ergocornine produced regression of tumor growth, degeneration of tumor tissue and suppression of prolactin but not GH secretion. Ergocornine is believed to inhibit prolactin secretion by a direct action on the pituitary tumor. Ergonovine also inhibited tumor growth but ergocryptine and a thalidomide-related compound, CG 603, both of which inhibit prolactin release by the normal in situ pituitary, had no effect on the size or secretory activity of the tumor.

7. Ergocornine and ergocryptine produced marked regression of spontaneous mammary tumors in old female rats. It was concluded that the ergot derivatives inhibited mammary tumor growth by depressing prolactin secretion.

8. The ergot derivatives, ergocornine and LSD, also inhibited growth of carcinogen-induced mammary tumors. The anticancer activity of ergocornine was enhanced by simultaneous treatment with ovariectomy or large doses of estradiol benzoate which further decreased prolactin secretion and/or interfered with the peripheral action of prolactin on mammary tumors, respectively.

9. Drostanolone propionate, a modified testosterone compound, was found to be a potent inhibitor of growth of carcinogen-induced mammary tumors in rats. However, its inhibitory effects on tumor growth were completely overcome by simultaneous injections of prolactin. It is suggested that high doses of androgens, like high doses of estrogens, inhibit mammary tumor growth by interfering with the peripheral action of prolactin on tumor parenchyma.

10. Convincing evidence was obtained that mammary tumor growth can be altered by altering catecholamine activity in the hypothalamus. Thus treatment with l-dopa or pargyline, which increases catecholamines in the hypothalamus and thereby reduce prolactin release, produced marked regression of established tumors and complete suppression of new tumor development. By contrast, methyldopa and haloperidol produced profound stimulation of mammary tumor growth. Both these drugs produce several fold increases in prolactin secretion by decreasing hypothalamic catecholamine activity. Order No. 74-13,956, 406 pages.

STUDIES ON EXTRARENAL ERYTHROPOIETIN PRODUCTION

RAPPAPORT, Ira Arthur, Ph.D.
New York University, 1973

Adviser: Dr. Albert S. Gordon

The experiments described in this thesis demonstrated that there is a rapid decline in the levels of plasma erythropoietin produced by nephrectomized rats in response to mild hypoxia (0.40 or 0.45 atmospheres of air for 6 hours) as the time between the operation and the hypoxia is prolonged. The decline was more rapid in males than females, but in both cases the ability to produce extrarenal erythropoietin in response to these stimuli was ultimately abolished. This could not be attributed to the development of uremia or acidosis since controls with ligated ureters developed similar changes in plasma chemistry without demonstrating a significant difference in renal or extrarenal erythropoietin production. The sex difference appeared to be due, at least in part, to the stimulatory effects of androgen since nephrectomized, orchidectomized rats showed a decline in erythropoietin production similar to that of nephrectomized females. Of importance is the fact that intravenous administration of small amounts of erythrogenin was sufficient to restore the erythropoietin response to mild hypoxia in long-term nephrectomized rats while having no effect on nonhypoxic controls. This suggests that the extrarenal erythropoietin production in response to mild hypoxia is dependent upon the hypoxic activation of small amounts of residual renal erythrogenin left in the circulation after nephrectomy. According to this concept, the progressive decline in erythropoietin production after nephrectomy would be due to the gradual plasma clearance of this residual renal erythrogenin. This mechanism does not appear to be the only one capable of functioning in the adult rat. Thus, a distinctly different response was observed in rats of both sexes when the hypoxic stimulus was of a greater intensity (0.35 atmospheres of air for 6 hours). It has been shown that under these more intense conditions, the liver, spleen and possibly other sites are capable of producing erythrogenin. The more sustained erythropoietin production observed in this study therefore appears to be due to the de novo production of extrarenal erythrogenin. The present experiments therefore point to the existence of two distinct mechanisms of extrarenal erythropoietin production. One mechanism is responsive to mild