

79. LHRH ANALOG THERAPY IN BOYS WITH TRUE PRECOCIOUS PUBERTY DUE TO HYPOTHALAMIC HAMARTOMA
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We have recently shown that a long-acting analog of LHRH suppresses pituitary gonadotropins and estradiol to prepubertal levels within 2 months in five girls with idiopathic precocious puberty (NEJM 305: 1546, 1981). Two boys with precocious puberty due to a hypothalamic hamartoma have now been treated for six months with D-Trp⁶-Pro⁹-NET-LHRH (LHRH_a) 4 µg/kg s.c. daily (supplied by W. Vale and J. Rivier of the Salk Institute). The boys had a mean testicular volume of 13 + 2 ml, Tanner III pubic hair, facial hair, and advanced bone ages. Hormonal results are shown below (mean + SE). Basal LH and FSH were measured every 20 minutes for 4 hours during the day and night. Peak LH and FSH refer to the maximum level during an LHRH test.

	Basal LH	Peak LH	Basal FSH	Peak FSH	T
before	6 + 2	65 + 25	8 + 4	26 + 13	196 + 28
6 months	3 ± 0.4	3 ± 0.4	0.8 ± 0.5	1 ± 0.7	13 ± 0

Basal and peak LH and FSH (mIU/ml), and testosterone (T,ng/dl) fell during LHRH_a therapy. Testis size decreased to 9 + 1 ml, pubic hair to Tanner II, and facial hair disappeared. Thus, LHRH_a caused favorable hormonal and clinical changes in boys with true precocious puberty. No adverse reactions were observed. We conclude that LHRH analog is an effective therapy for boys with true precocious puberty.

80. POTENT ANTIGLUCOCORTICOID ACTIVITY OF RU38486 ON ACTH SECRETION IN VITRO AND IN VIVO IN THE RAT

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ACTH release in rat adenohypophysial cells in culture is a highly specific, sensitive and reliable bioassay for glucocorticoid agonists and antagonists, no interference being observed with estrogens, androgens and progestins. In this system, RU38486 is the most potent of a series of steroid derivatives to reverse the inhibitory effect of dexamethasone on 8-Br-cyclic AMP-induced ACTH release at an ED₅₀ value of 1.5 nM. The compound has no agonistic activity up to 1 µM (the highest concentration studied). After oral administration of RU38486 (100 mg/kg), plasma ACTH levels reach a maximum (from 25 ± 5 to 450 ± 80 ng/ml) at 2h and are still elevated at 6h (135 ± 40 ng/ml, p < 0.01). A significant stimulatory effect of RU38486 on plasma ACTH and corticosterone secretion is observed at the 15 mg/kg dose. Increased basal plasma ACTH levels induced by the antagonist can be completely reversed within 2h by the administration of dexamethasone. The present data show that RU38486 is the first highly potent and orally active glucocorticoid antagonist.

81. CORTICOTROPIN-RELEASING FACTOR BINDING AND ACTIVATION OF ADENYLATE CYCLASE IN THE ANTERIOR PITUITARY GLAND. Lefèvre, G., Gagné, B., Lavoie, M., Lefebvre, F.A. and Godbout, M., Department of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada.

Ovine corticotropin-releasing factor (CRF) stimulates adenylate cyclase activity in rat anterior pituitary homogenate at an ED₅₀ value of 70 nM. GTP potentiates the stimulatory effect of CRF on [³²P] cyclic AMP formation in a rat adenohypophysial particulate fraction and in bovine adenohypophysial membranes at an ED₅₀ value of 0.1 µM. [¹²⁵I]CRF binds to a single class of high affinity sites in bovine adenohypophysial plasma membranes at a dissociation constant (K_D value) of 1 nM, the number of binding sites being 320 fmoles/mg protein. Divalent cations (Ca²⁺, Mg²⁺ and Mn²⁺) exert a marked effect on CRF binding, the stimulatory effect observed at 1 to 2.5 nM, being followed by inhibition at higher concentrations. In the presence of Mg²⁺, the binding of CRF is rapid, fully reversible and localized mainly in plasma membranes. GTP exerts marked inhibitory effects on CRF binding, the K_D value being increased 10-fold. The present data show that activation of the CRF receptor stimulates adenylate cyclase activity in rat and bovine anterior pituitary gland at least partly through a guanyl-nucleotide dependent mechanism.