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DOES LHRH-AGONIST ACT THROUGH ACTIVATION OF PHOSPHOLIPASE C?

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The pituitary decapeptide LHRH and its agonists (LHRH-A) can stimulate steroid production in isolated rat Leydig cells. The mechanism of action of LHRH is not yet clear, whereas it is known that LH action involves cAMP and Ca^{2+}. We have investigated whether LHRH acts via phospholipase C (PL-C), by comparing the effects of LHRH-A and PL-C on basal and LH-dependent steroid production, protein phosphorylation and protein synthesis by rat Leydig cells.

Leydig cells from 21-24 day old rats were incubated for 3 h in all experiments. LH (100 ng/ml), LHRH-A (40 nM; HOE766) and PL-C (1 U/ml) stimulated steroid production (25-, 5- and 4-fold, respectively). LHRH-A and PL-C acted synergistically with LH and stimulated steroid production 50-fold. LH stimulated the phosphorylation of a 17 kD nuclear protein and the 33 kD ribosomal protein S6. Stimulated protein phosphorylation could not be detected in the presence of LHRH-A or PL-C. LHRH-A and PL-C alone had a small stimulatory effect, but acted synergistically on the the synthesis of a 14, 27 and a 70 kD protein. Phospholipase A_2 did not have an effect in all experiments.

The similarities between the effects of LHRH-A and PL-C on steroidogenesis, protein phosphorylation and protein synthesis suggest that the primary effect of LHRH is activation of hydrolysis of phospholipids. This phospholipid breakdown may cause changes in membrane fluidity, or activate PK-C and IP_3 mediated liberation of Ca^{2+} from specific intracellular pools. Arachidonic acid metabolites probably have no important role, since PL-A_2 has no effects.

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PHARMACODYNAMICS, PHARMACOKINETICS AND BIOAVAILABILITY OF THE PROLONGED LH-RH AGONIST DECAPEPTYL-SR

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During a therapeutic study on palliative treatment of prostatic carcinoma with Decapeptyl-SR (DP-SR) (Ferring, Kiel, FRG), serum concentrations of LH, testosterone (T) and Decapeptyl (DP) were measured by RIA in 8 patients with prostatic carcinoma who received 4 mg DP-SR every 5 weeks i.m. for 7.5 months. DP-SR is D-Trp^6-LH-RH (DP) in a sustained release (SR) formulation (D-lactide glycolide copolymere). DP was also infused i.v. to healthy male volunteers at a rate of 4, 8, and 16 ug/h for 90 min (n=5) and a rate of 16 ug/h for 180 min (n=2).

Within 2 to 3 weeks after the 1st injection of DP-SR, serum LH decreased below 10 mIU/ml in the patients and serum T reached castrate levels, i.e. 0.2 to 0.8 ng/dl. This effect was maintained by repeated injections every 5 weeks. Highest DP serum levels ($\bar{x}$=1700 pg/ml) were measured 3 hours after the injection. Thereafter, serum DP decreased quickly ($t_{1/2\alpha}$=4.8 h). This was followed by a slow decrease of serum DP from about 500 pg/ml during the 1st week after the injection to 50 pg/ml after 5 weeks. During repeated application of DP-SR, a slight cumulation was found (minimum concentration about 400 pg/ml). After termination of the infusions in normal men the peptide was eliminated at a rate of 0.8 h^{-1} corresponding to a biological half-life of 51.7 min. A comparison of the areas under the curves of serum DP after the injection of DP-SR with the extrapolated data of the infusion studies results in a bioavailability of about 1 for DP-SR.

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ANDROGEN LEVELS IN PROSTATIC TISSUE OF PATIENTS WITH CARCINOMA OF THE PROSTATE TREATED WITH THE COMBINED THERAPY USING AN LHRH AGONIST AND A PURE ANTIANDROGEN

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It is well known that treatment with LHRH agonists induces a complete blockade of testicular steroidogenesis and causes a decrease of plasma androgens to castration levels. The combination of an antiandrogen to castration (chemical or surgical) blocks the action of residual androgens in the prostate and, in addition, reduces the serum levels of C-19 steroids (dehydroepiandrosterone and its sulfate) by approximately 50%. In the present study, we have compared the levels of testosterone (T), dihydrotestosterone (DHT) and androstane-3α,17β-diol (3α-diol) in prostate tissue from untreated patients, castrated patient and patients receiving the combined therapy.

Treatment	T	DHT	3α-diol
	(ng/g)		
Untreated (n=6)	1.42±0.1	4.2±0.5	0.70±0.2
Castrated (n=5)	1.13±0.3	1.7±0.6	4.21±1.5
Combination therapy (n=3)	0.45±0.2	< 0.3	0.35±0.1

Our preliminary data indicate that the addition of an antiandrogen to castration has an inhibitory effect on prostatic androgen levels and offers an additional explanation for the higher rate of response and increased duration of the response in patients receiving the combined therapy when compared to castration alone.

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DOSE RESPONSE TITRATION OF DECAPEPTYL IN TREATMENT OF CARCINOMA OF THE PROSTATE

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Decapeptyl(D-Trp-6-LHRH analalogue) has recently become available in a sustained release microsphere form for monthly injection. In an attempt to assess the endocrine effects of this compound twenty patients randomised to either 50,100,200ug of Decapeptyl or Stilboestrol have been followed with serial measurements of testosterone for two months. A total of 76 injections have been given without any serious local problem, though the majority of patients experienced some minor discomfort while the injection was being given. There was no obvious difference in the effects of the treatments in terms of disease control (2/5 receiving 200 ug, 3/5 receiving 100 ug, 2/5 receiving 50 ug have had disease response with clinical remission beyond two months as have 3/5 receiving stilboestrol. To date the initial measurements of testosterone have been similar in all three Decapeptyl arms, though a biochemical surge in testosterone levels only occurred in 3/5 receiving 50 ug compared to 5/5 receiving 100 ug and 5/5 receiving 200 ug. After two treatments there was no significant difference in mean testosterone levels between the groups though there was a trend for a lower mean the higher the dose of Decapeptyl (50mg: 1.7, 100mg: 1.4, 200mg: 1.2 stilboestrol 1.1 nmol/l).