The Effects of Continuous Sustained Release of DHEA and DHEAS on Male Rat Reproductive Tissue

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Introduction: Dehydrepiandrosteone (DHEA), is a natural precursor steroid hormone produced by the adrenal gland. During development into adulthood, massive levels of DHEA simply metabolize into other hormones such as estrogen (E) and testosterone. Yet with advanced age, there is a tremendous decline in the secretion of this hormone which is known to be linked to conditions such as; diabetes, hypercholesterolemia, obesity, multiplesclerosis, cardiovascular disease, parkinson's disease, alzheimer's' disease, autoimmune disorders, depression, and osteoporosis.

It was documented that DHEA administration may increase estrogen or testosterone in the peripheral tissue, and their affects may be tissue specific. The simple fact is that not much is known about DHEA or its sulfated form (DHEAS). The aim of this study was to evaluate, for the first time, the cytopathological changes of the male rat reproductive tissues exposed to sustained delivery of DHEA or DHEAS using ceramic drug delivery system. Our hypothesis states that exposure of physiological and sustained levels of DHEA or DHEAS by means of triclacium phosphate-lysine (TCPL) ceramic drug delivery system will induce differentiation of epithelial like cells in hormone responsive tissue such as the ventral prostate of adult rodents. The specific objectives of this study were to (i) investigate the pathophysiological responses associated with sustained delivery of physiological and supraphysiological levels of DHEA on the testes, seminal vesicles, ventral prostate and epididymis, (ii) the role of sustained delivery of physiological levels of DHEAS on the same tissues. Results of the investigation can be used as a diagnostic tool to study the conversion of adrenal agents in the periphery.

Material and Methods:

Animals and Housing: A total of 20 Sprague Dawley rats weighing 250-300 gm were divided into 4 groups of 5 rats each. Group I animals were implanted with TCPL containing 200 mg (Low Dose) of DHEA, Group II animals were implanted with 600 mg of DHEA (high Dose) and group III was implanted with capsules containing 200 mg of DHEAS. Group IV animals were implanted with empty capsules and served as a control (sham) group.

TCPL ceramic drug delivery system fabrication: The microcrystals of calcium-phosphate were prepared by following standard laboratory procedures. The sintered TCP powder, was combined with lysine to act as a binder (TCPL), and then mixed with DHEA or DHEAS. The mixture was cold pressed into cylindrical form (final density of 1.71 ± 0.11 gm/cm³ and surface area of (3.54 ± 0.11 cm²) using a 3/8" die set at a compression load of 2500 Kg [Benghuzzi and Bajpai].

Surgical Implantation: The use of animals and surgical implantation procedure was approved by the University of Mississippi Medical Center IACUC Committee. Rats were anesthetized with xylazine/ketamine and their abdomens were shaved and scrubbed with providone iodine for intraperitoneal (IP) implantation. The site of incision was closed with deep sutures and superficial wound clips. All rats that underwent surgical implantation received an injection of 0.1 ml of 200,000 units of Penicillin G post-operatively.

Histopathological Evaluation: All rats were sacrificed at the end of 28 days post-implantation and reproductive and vital organs were removed, weighed and stored in 10% formalin for histopathological evaluation.

Statistics and Graphics: Descriptive statistics and analysis of variance were performed using Sigma Stat Software.

Results and Discussion:

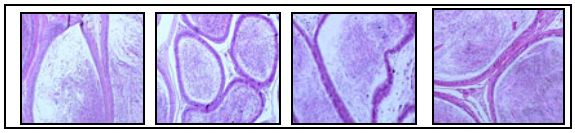
Results obtained from this study demonstrated the use of TCPL as a carrier to deliver DHEA-Low dose (5 ng/ml), DHEA-High dose (15 ng/ml) and DHEAS (5 ng/ml) resulted in several pathophysiological conditions. There were no significant increases or decreases in body weight between the experimental groups and the control group. A 22% reduction in kidney weight was observed in all rats treated with DHEAS or DHEA regardless of dose. This information suggests that the kidney is an important target tissue for DHEA and DHEAS. The reproductive tissue wet weights are displayed in Table 1. The results show decreased prostate, testicular and seminal vesicle weights with increased wet weights of the epididymis. The data suggest that DHEA or DHEAS administration act in a similar fashion to exogenous administration of testosterone. When testosterone was administered exogenously in an intact system there was a remarkable reduction in the reproductive organs (previous documented study). The data obtained suggests the possibility that DHEA and DHEAS are converted to testosterone and the action on the reproductive system is due directly to testosterone and not the precursors DHEA or DHEAS.

Table 1: Mean Reproductive organ weight in gm ± SD

Groups	Testes	Sem Ves	Prostate	Epidid
DHEA -L	3.2 ± 0.3	0.77 ± 0.08	0.52 ± 0.12	1.1 ± 0.9
DHEA-H	3.4 ± 0.8	0.83 ± 0.06	0.50 ± 0.08	1.2 ± 0.12
DHEAS	3.3 ± 0. 7	0.80 ± 0.11	0.42 ± 0.07	1.2 ± 0.06
Control	4.2 ± 0.8	2.3 ± 1.35	0.96 ± 0.33	0.68 ± 0.6

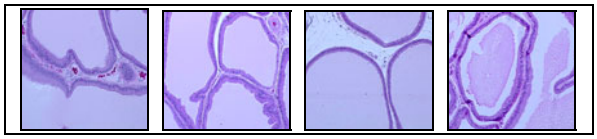
Histopathological evaluation of the tissue collected from the animals revealed significant morphological changes between the groups. In the prostate there was an atrophy pattern in the experimental groups compared to the control group. The experimental group also showed occasional hypertrophy in the tubules of the epididymis compared to the control group.

EPIDIDYMIS



DHEA –L DHEA-H DHEAS Control

PROSTATE



DHEA –L DHEA-H DHEAS Control

Conclusions: The results of this study demonstrated the followings:

(1) DHEA and DHEAS can be delivered by TCPL delivery systems at sustained levels for long duration.

(2) DHEA and DHEAS induced structural and functional changes on the kidney and reproductive tissues of male rats when delivered for 28 days in a sustained fashion.

(3) Additional studies are needed to determine the mode of action of these agents and to asses if the histopathological changes are a direct result of DHEA or DHEAS or an indirect result to the conversion to an active precursor such as testosterone or dihydrotestosterone.

References:

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