MRI Assessment of the Growth Effects of Anabolic Steriods in Guinea Pig Model

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INTRODUCTION

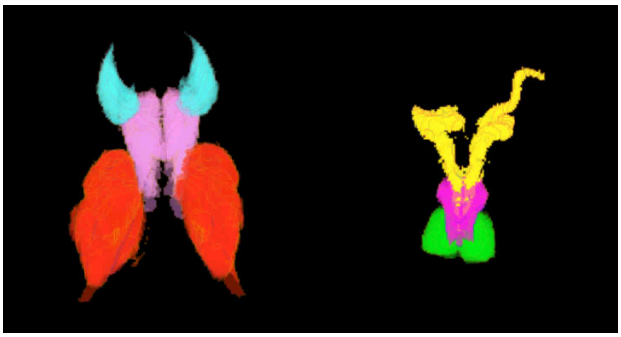
Androgens, or anabolic steroids, are now widely used by professional and recreational athletes, weight lifters and bodybuilders, and non-athletes wishing to enhance their appearance and physical performance despite their known adverse effects, unknown long-term risks, and abuse potential. Experimentally, the effects of anabolic steroids on muscle growth and body composition were previously investigated in intact and castrated the guinea pigs using dissection method, revealing an increase of muscle mass (Kochakian CD *et al*. 1956, 1957). The overall goal of this project is to establish and employ an MRI protocol to quantitatively evaluate and characterize the growth effects of various anabolic steroids in a guinea pig model.

METHODS

Animal and Treatment Protocol 12-wk old male Hartley guinea pigs were employed. All were implanted with subcutaneous silastic capsules for steroid administration or as sham control. Animals were divided into four groups and imaged at three time points, i.e., baseline, wk-8 and wk-16 post the implantation. They were (1) Intact animal with Empty capsule, N=16; (2) Castrated with Empty capsule, N=17; (3) Intact with Nandrolane capsule, N=18; (4) Castrated with Nandrolane capsule, N=18; (5) Intact with Testosterone, N=19; and (6) Castrated with Testosterone, N=14. The dosage schedule of nandrolane and testosterone was first determined in a pilot study using blood sampling and analysis over 80-day period.

MRI Image Acquisition 3D high-resolution images were acquired to cover the entire body of each guinea pig with a coronal multi-slice T1W sequence (0.5mm X 0.5mm X 1.5mm voxel size) on a whole-body 1.5T scanner using a 10cm I.D. quadrature coil. Such images provide adequate soft tissue contrast for delineation of muscle, fat, and organs. Animals were anesthetized with IP injection of 30 mg/Kg sodium pentobarbital during imaging.

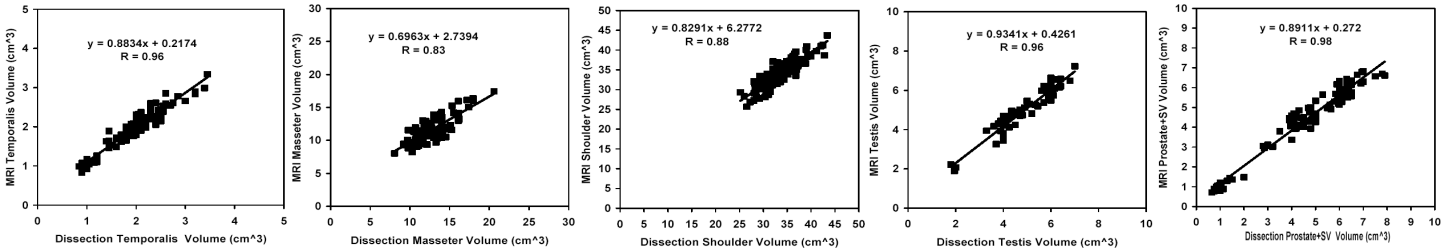
MRI Image Analysis Images were analyzed using an IDL based customized software package. It features fast semi-automatic and interactive segmentation using a combination of intensity and histogram based, 2D & 3D region growing, and active contouring algorithms for effective tissue separation and labeling. Nine tissue compartments were labeled and quantified based on boundaries detectable in the whole body MR images, which included the mass of five skeletal muscles in specific segments (temporalis, masseter, neck complex, shoulder complex, and the remaining skeletal muscle), three sexual organs (prostate and seminal vesicles, testis), and whole-body adipose tissue. The boundaries of these regions were defined stereotaxically based on anatomical landmarks identified using a standard guinea pig anatomy atlas (Cooper G and Schiller AL, 1975). The growth effects were statistically analyzed and compared between and within groups.



Validation of MRI Protocol All animals were sacrificed at end point and dissection analyses were performed. Accuracy of MRI acquisition and analysis protocol was validated by comparing MRI and dissection data.

RESULTS

MRI protocol employed in this study permits the delineation and quantitation of target muscles and organs. The figure (right) illustrates a set of segmented masseter, neck muscle, should muscle, prostate, seminal vesicles, and testis in an intact adult guinea pig. Excellent correlations were found between in vivo MRI measurement and postmortem dissection analyzes at the end point (see figure below).



Muscle and Organ Growth Effects Significant and substantial differences were observed for all of the comparisons made between the Intact and Castrated Empty capsule groups. More importantly, steroid replacement in the castrated groups resulted in significant growth to or towards normal for all muscles and prostates with the exception of the shoulder complex at both wek-8 and wk-16 (see table to right for statistical significances).

Significant effects between castrated empty group and castrated drug treated groups at Midpoint and Endpoint

		MRI Measurement						
Group comparison		Total AT	Total Muscle	Pros.+ S.V.	Neck	Masseter	Temporalis	Shoulder
Castrated Empty vs. Castr. Testos	time2	0.0241	0.0033	<0.0001	0.0002	0.0035	<0.0001	0.01
	time3	0.0075	0.001	<0.0001	<0.0001	<0.0001	<0.0001	0.106
Castrated Empty vs. Castr. Nand.	time2	0.2627	0.002	<0.0001	<0.0001	<0.0001	<0.0001	0.0024
	time3	0.0323	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0687

Total Body Skeletal Muscle and Fat Growth Effects Castration led to significant reductions of total skeletal muscle, but not total adipose tissue, at midpoint and endpoint in the Castrated Empty capsule group, in comparison with the Intact Empty capsule group. In contrast, hormone replacement in the Castrated Testosterone capsule group completely normalized the growth of skeletal muscle at these points.

Conclusion A castrated guinea pig anabolic test model using an MRI acquisition and analysis protocol was successfully demonstrated here. Highly significant differences of muscle and organ growth were detected between intact and castrated guinea pigs in a 16-wk nandrolane and testosterone treatment protocol. The model was validated for future quantitative testing of other potential anabolic agents. MRI measurements appear more sensitive to potential differences in muscle growth than the dissection study, and offer the ability to assess growth at multiple time points in the same set of animals.