

# Creatine monohydrate as a supplement.

Do we know what we are doing?

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# What is a supplement?

- To fill up or supply by additions; to add something to; to fill the deficiencies of.
- These substances can be legal or illegal.
- It is important to note that none of the legal supplements are subjected to quality control, nor do they have to provide proof of their claims.



# Where do we get supplements?

- There are about 170 companies in South Africa supplying various supplements to the market, as varied as colostrum and queen jelly to prohormones and creatine monohydrate.
- One example is USN, they alone supply 231 different supplements.

# Why use a supplement?

- To increase the ergogenic effect of exercise, to run faster, jump higher, or throw further than the competition.
- To increase the androgenic effect of resistance training.
- The supplement in this case is creatine monohydrate.



# What is an ergogenic aid?

- It's defined as any means of enhancing energy utilization, including energy production, control, and efficiency.
- Athletes frequently use ergogenic aids to improve their performance and increase their chances of winning in competition.

# Ergogenic effect.

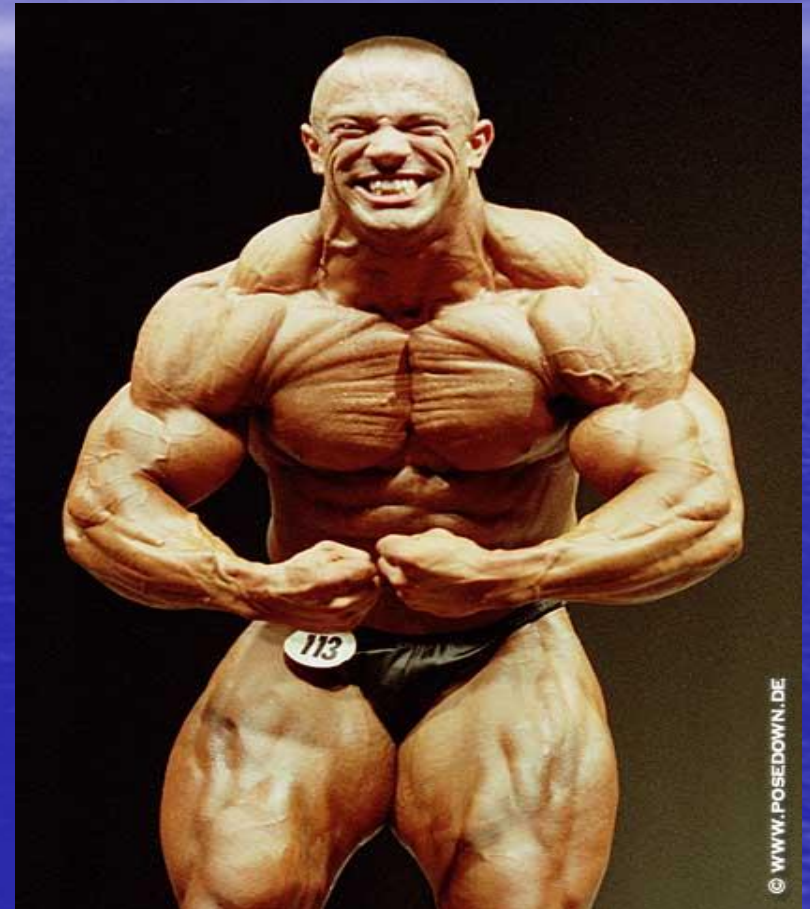
- Short term benefit only.
- Increased phospho-creatine at site of need.
- Possible faster recovery after exercise.
- Acts as a pH buffer, therefore prevents lactic acid buildup, delaying fatigue.



# Androgenic aid

- Defined as a supplement to increase the muscle building effect of resistance training by any means, because some people actually wants to look like....

# This





# What are the factors we need to look at ?

- Creatine monohydrate.
- Pluripotent stem cells.
- Satellite cells.
- Androgen receptors.
- Testosterone.
- Dihydrotestosterone.
- Resistance training.
- Is there interaction between the above?

# Creatine monohydrate.

- Chemically: methyl guanidine-acetic acid.
- Creatine from dietary sources provide approximately 1-2 g of creatine per day.
- 1-2 g per day is synthesized from amino acids, arginine, glycine, and methionine in the human liver, kidney, and pancreas.



# History.

- Discovered 1832. First organized use 1992 by the British Olympic team.
- Marketed as an ergogenic and androgenic aid.
- Supplementation of creatine, was a \$200 million a year industry in the USA in 1998.

# Muscle creatine content.

- Intramuscular levels of creatine 110-160 mmol kg<sup>-1</sup> dry muscle with ~60% of total creatine in the form of phospho creatine.
- Little creatine is found at the site of use, and therefore creatine must be transported from areas of synthesis to areas of storage and utilization.



# Creatine and muscle.

- Uptake is muscle fiber-type dependent.
- Type 2 fibers have higher levels of creatine and phosphocreatine.
- Exercise can stimulate the muscle uptake and content of creatine.
- Exercise increases the translocation of the creatine transporter to the muscle membrane.

# Creatine uptake.

- Uptake into muscles occurs via a sodium / chloride dependent transporter, (CreaT) against a concentration gradient, regulated by the intracellular concentration of creatine.
- Potential down-regulation of these systems with chronic exposure to creatine?
- Potential up regulation of transporter system?



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# Pluripotent stem cells.

- They are mesenchymal cells, embryonic stem cells (ESC), or somatic stem cells (SSC) that can be stimulated to develop into any tissue under the correct stimuli.
- It is widely distributed in the human body.
- Hormonal stimulation occurs via the androgen/estrogen receptor.
- Pluripotent stem cell stimulation in one direction inhibits the proliferation in the other line.



# What are the factors we need to look at ?

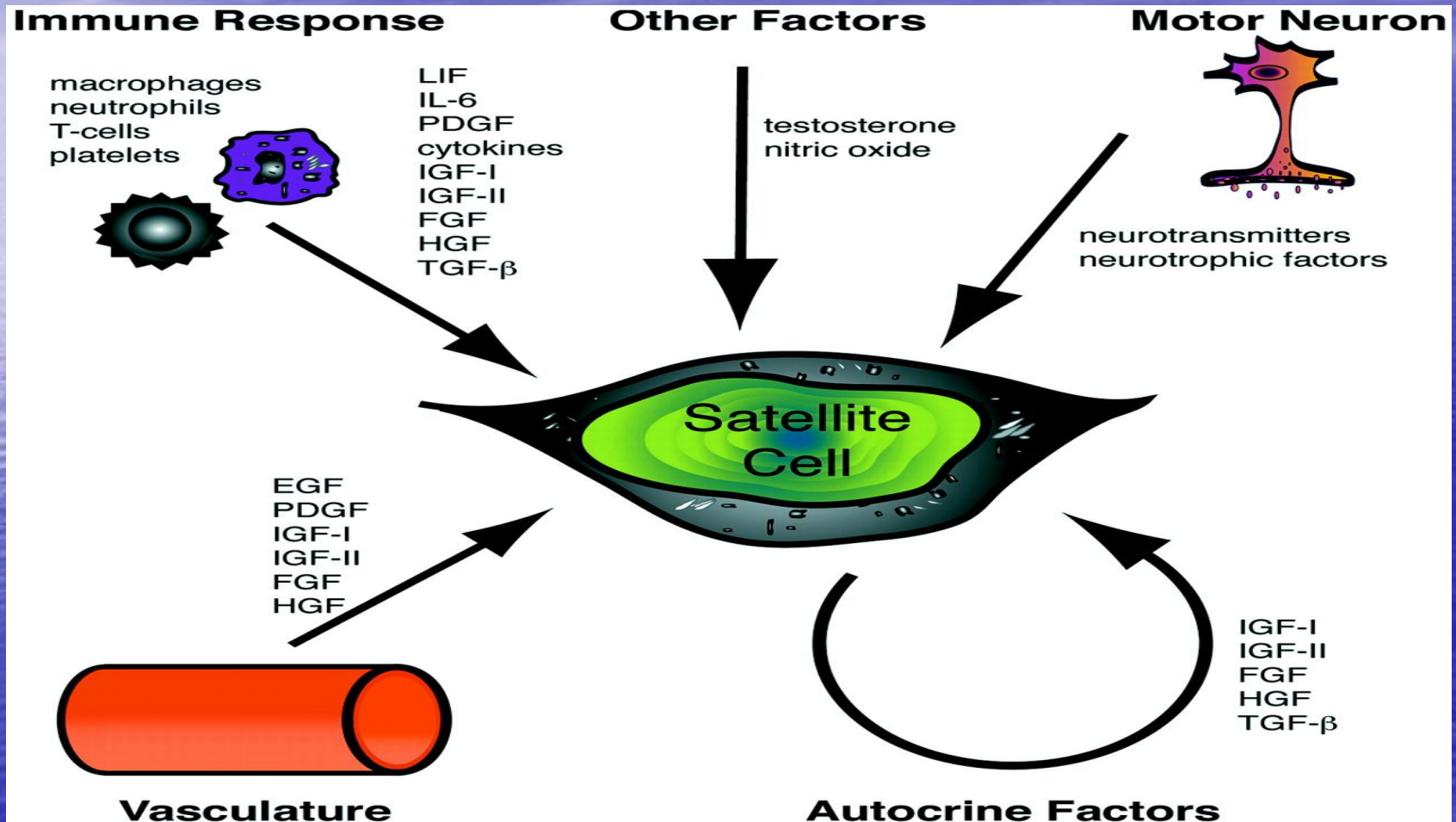
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# Satellite cells.

- “Specialized” pluripotent stem cells.
- These are cells or clusters of cells outside the basil lamina that ensheathes each muscle fiber.
- They have the potential to form new muscle under the correct stimuli.
- Various factors can produce this stimulus.



# Factors stimulating satellite cells.



# What are the factors we need to look at ?

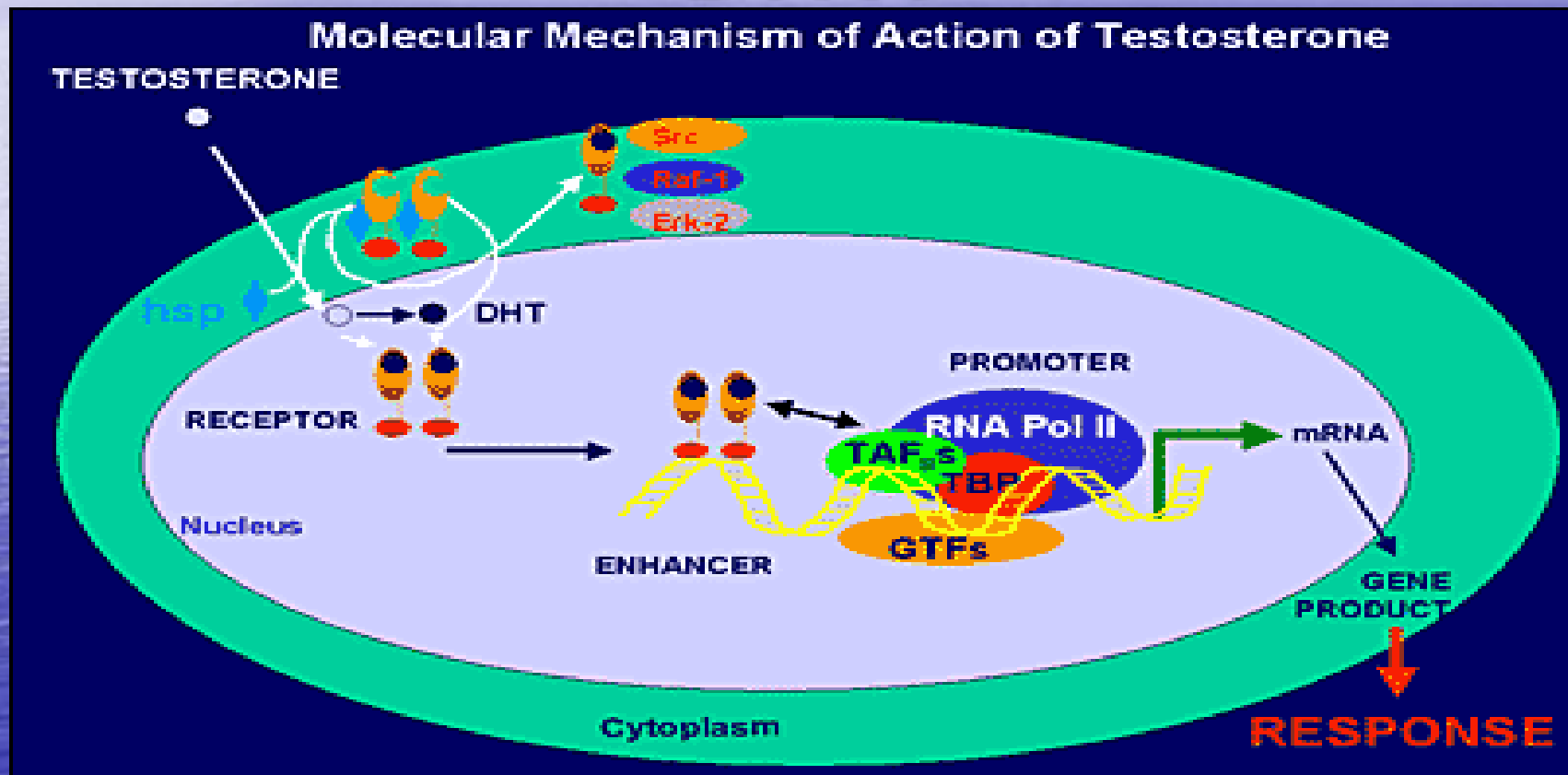
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# Androgen receptors.

- The receptors by which the androgen hormones exert their effect.
- Where are they located and how do we know that they are responsible for the androgenic effect?
- Can their density be influenced?

# Molecular mechanism of action of Testosterone and DHT.





# How do we know that they are responsible for the androgenic effect?

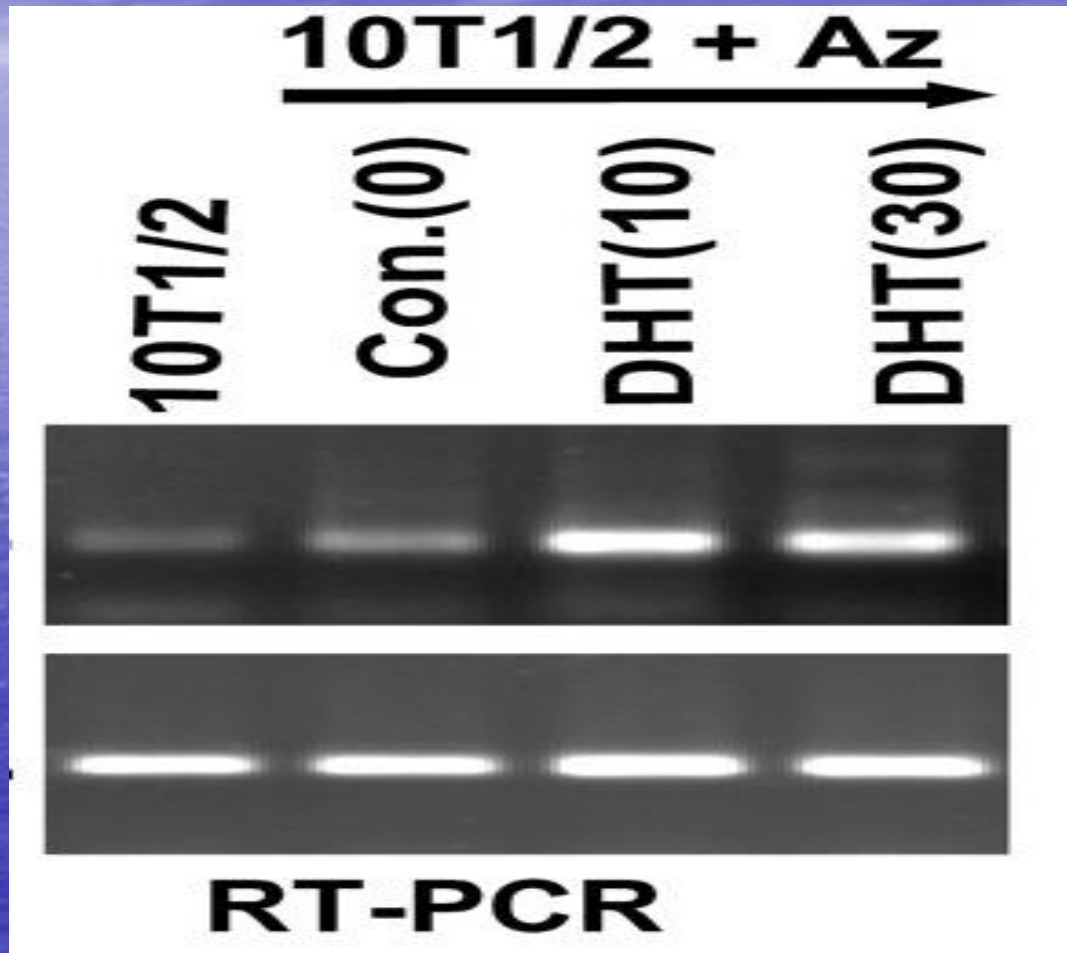
- In pluripotent stem cell cultures, androgen receptor mRNA and protein levels were low at baseline but increased after testosterone or DHT treatment.
- The effects were blocked by bicalutamide.

# Can the density of AR's be influenced?

- Down regulation due to immobility.
- Up regulation by:
  - Exercise.
  - Supra physiological doses of testosterone/DHT.
  - Additive effect of increased androgens and exercise.



# AR induction by androgens.

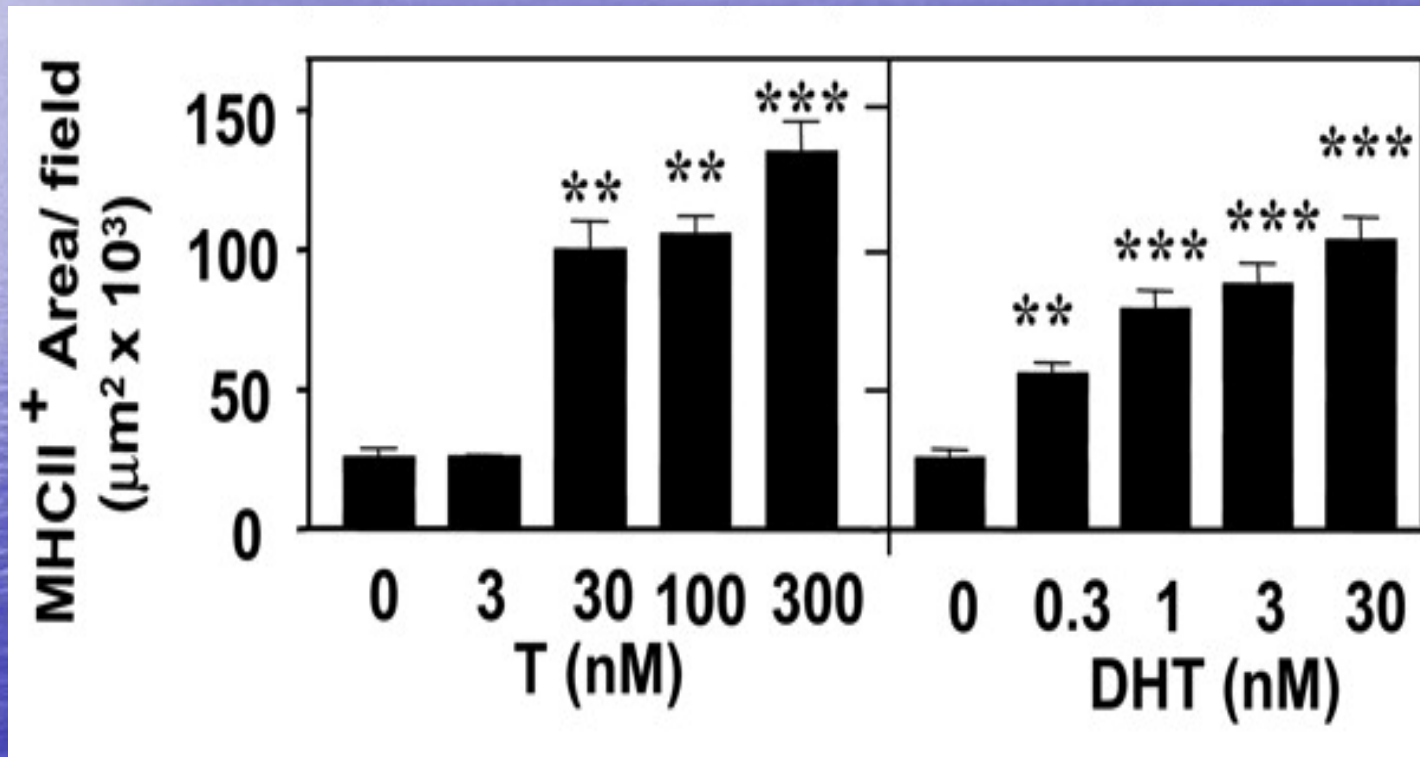


# How does Testosterone/DHT exert their androgenic effect?

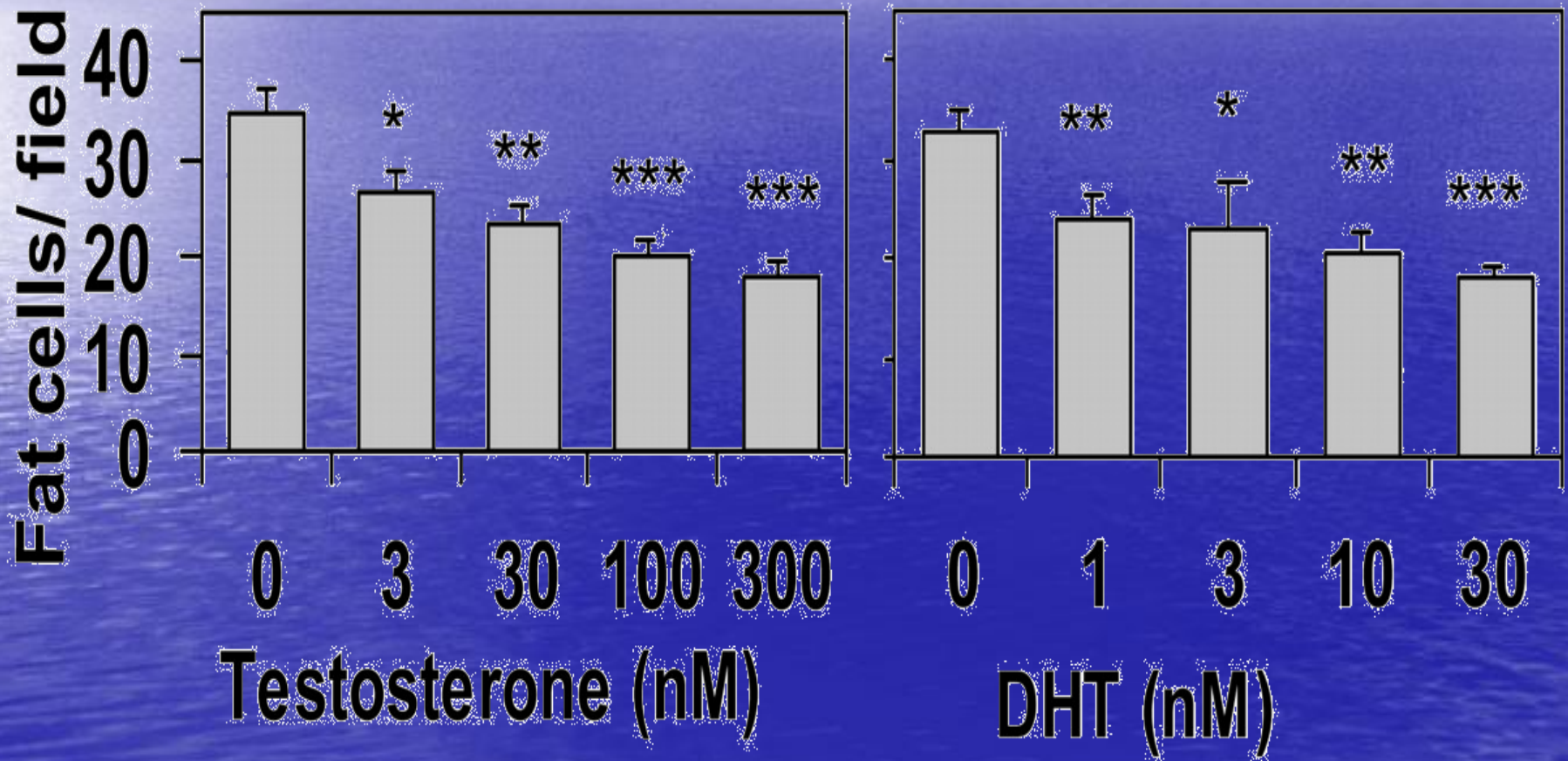
- Testosterone and DHT regulate lineage determination in mesenchymal pluripotent cells/satellite cells by promoting their commitment to the myogenic lineage and inhibiting their differentiation into the adipogenic lineage.



# The effect of supra physiological doses of androgens and AR induction.



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- **Testosterone.**
- Dihydrotestosterone.
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# Testosterone.

- The male androgen responsible for secondary male characteristics acting via the androgen receptor.
- Strength training combined with supra physiological doses of testosterone enhances muscle hypertrophy.
- % of the secreted testosterone is converted to dihydrotestosterone by the enzyme 5 alpha reductase.



# Conversion of Testosterone to Dihydrotestosterone

5 alpha reductase



Testosterone

Dihydrotestosterone



$\text{NADPH} + \text{H}^+$

$\text{NADP}$

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# Dihydrotestosterone.

- This is the most potent androgen in males and females.
- DHT 's affinity for the androgen receptor is 2-5 times that of testosterone, and has a 3-10 fold greater molar potency as a transactivator of the receptor.

# What are the factors we need to look at ?

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- **Resistance training.**
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If you want to look like this, you have to do resistance training.

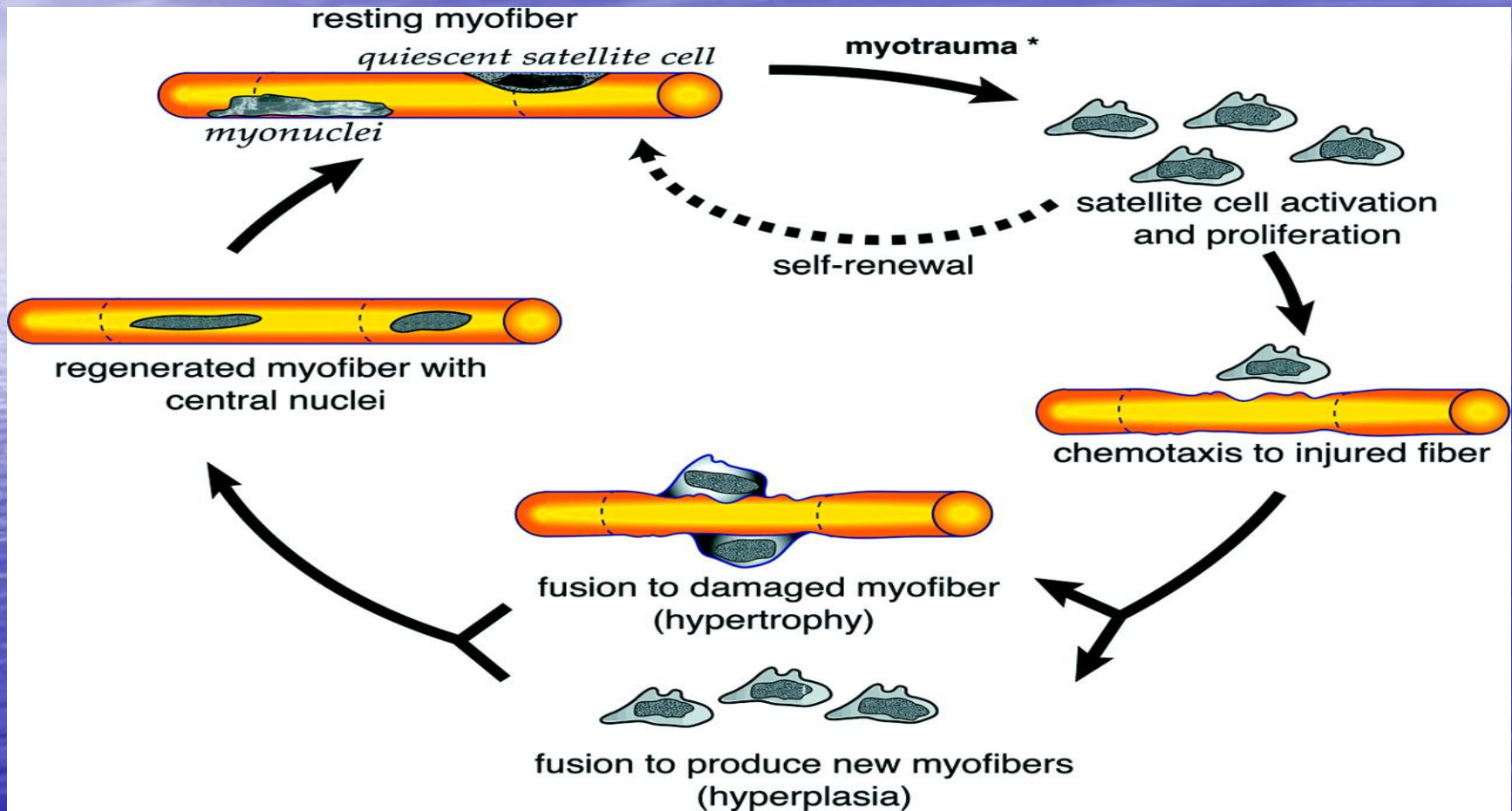


# What happens during resistance training?

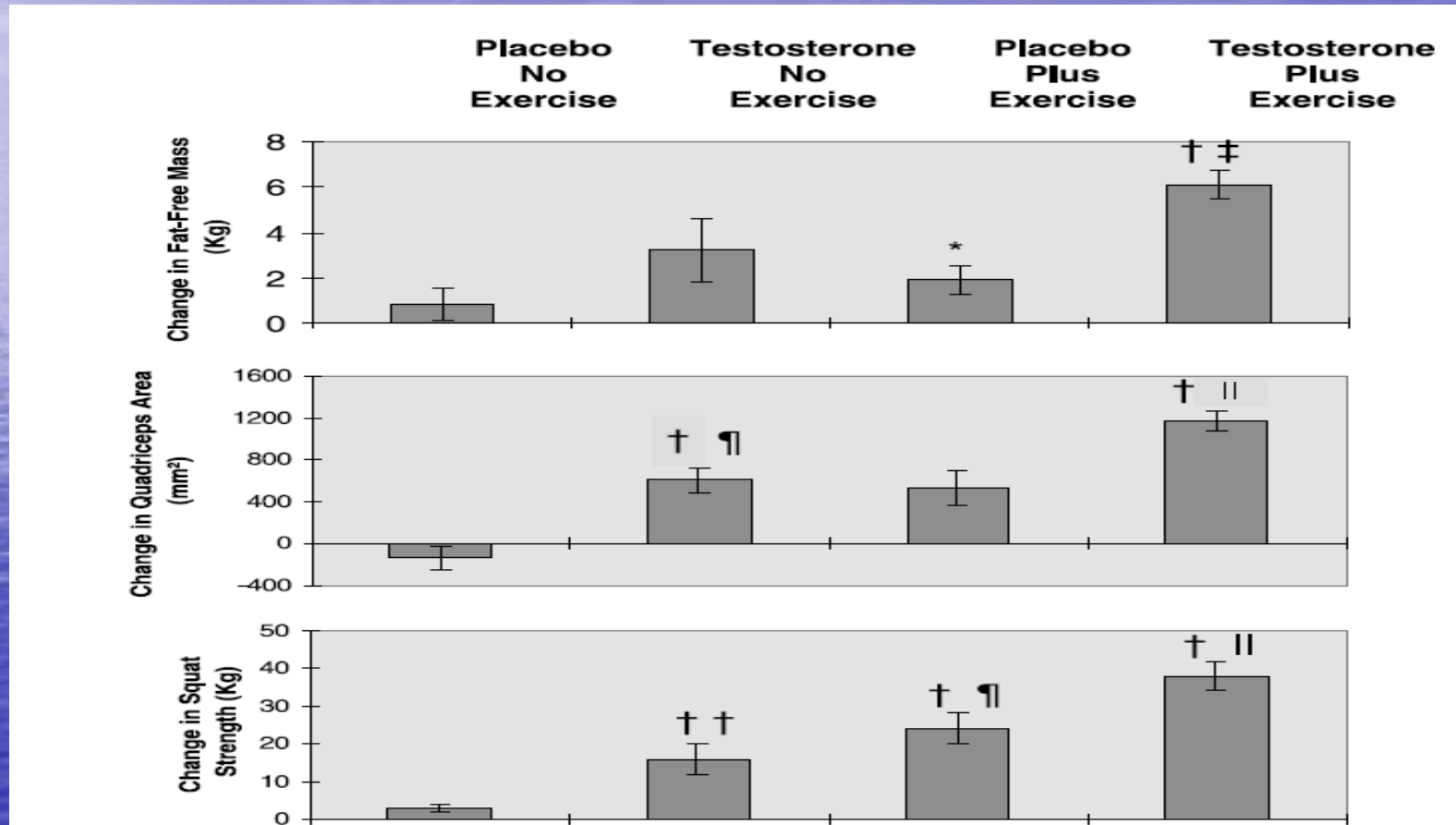
- Micro muscle damage.
- Increased Testosterone/Dihydrotestosterone.
- Resistance training increases satellite cell numbers and activity.
- Increases AR receptors.
- Muscle hypertrophy/hyperplasia.



# Satellite cell response to Myotrauma.

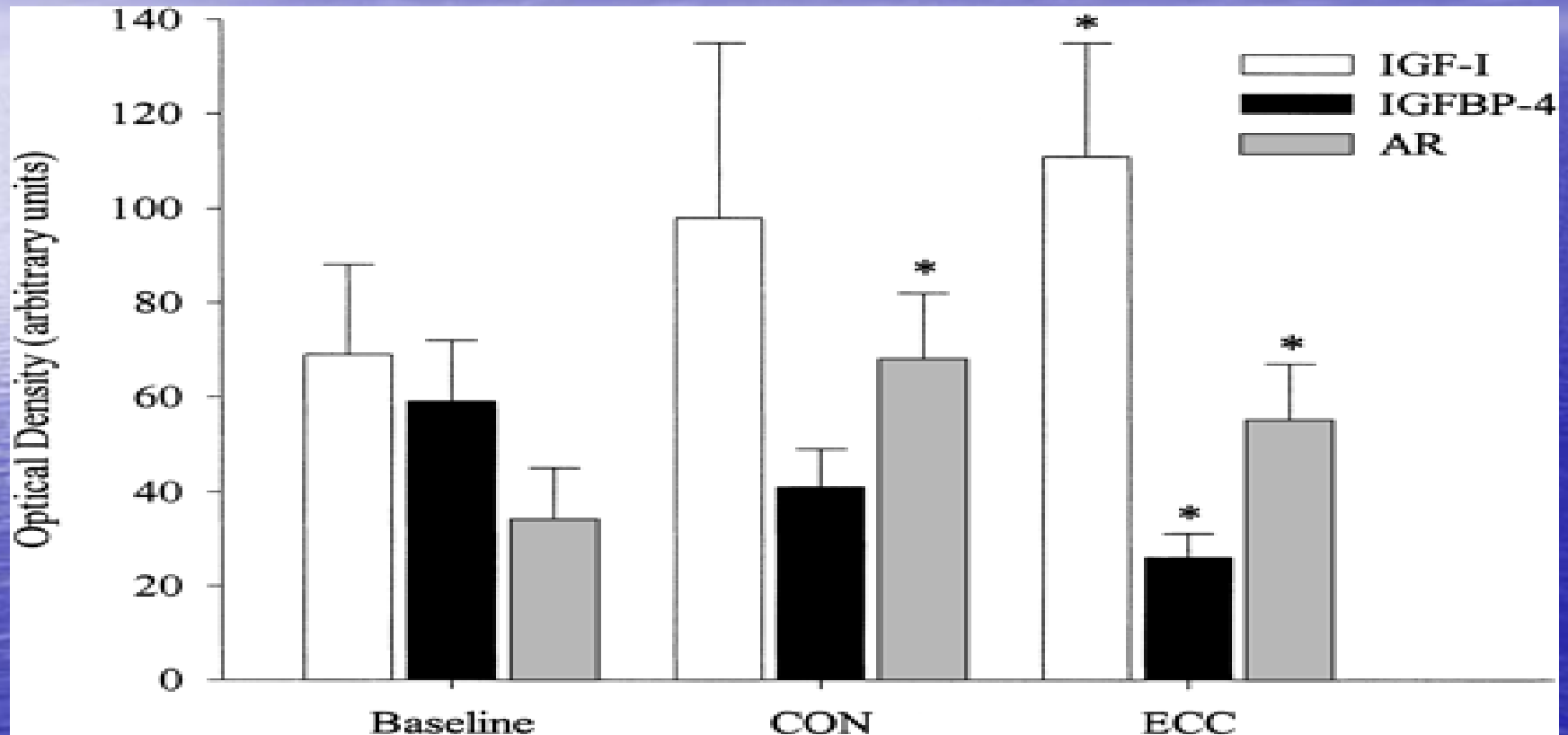


# Additive effect of androgens and resistance training.





# Resistance training increases the density of AR's.



# Where do supplements, especially creatine fit into this?

- Creatine has a remarkable androgenic effect in 33% of users, a small effect in 33% of users and no effect in 33%.
- The mechanism of the androgenic effects and the reason for this variable response is unknown, or is it?
- Various theories have been put forward to explain the androgenic mechanism of creatine supplementation.



# Theories.

- From the literature, the increase in muscle mass may result from:
  - Increased protein synthesis.
    - Hyper hydration / Creatine, an end product of contraction stimulates protein synthesis.
  - Reduced protein catabolism.
    - Creatine supplementation reduces exercise-induced muscle damage / Creatine supplementation increases ATP reserve, preventing transient ischemia, maintaining cell wall integrity.

# Are these theories the answer?

- No they do not explain the underlying mechanism for the androgenic effect seen in susceptible individuals.
- By asking why, did I find the answer, or simply add more questions?



# What is the answer?

- Double blind cross-over study.
- Leg one to last 3 weeks, then 6 weeks washout, followed by leg two also to last 3 weeks.
- Blood sampling and anthropometric measurements on day 0, day 7, day 21 during each leg.

# Study protocol.

- Tried to mimic actual use of creatine by:
- Not interfering with subject diets.
- Allowing normal training programs as done at the SA Rugby Institute at the University of Stellenbosch.
- Supplying creatine/glucose to be taken.



# How is creatine used?

- Loading phase, 25gm of creatine + 25gm of glucose.
- Maintenance phase, 5gm of creatine + 25gm glucose.
- In responders better results are obtained if supplementation is combined with strength training.

# What was the hypothesis to be tested?

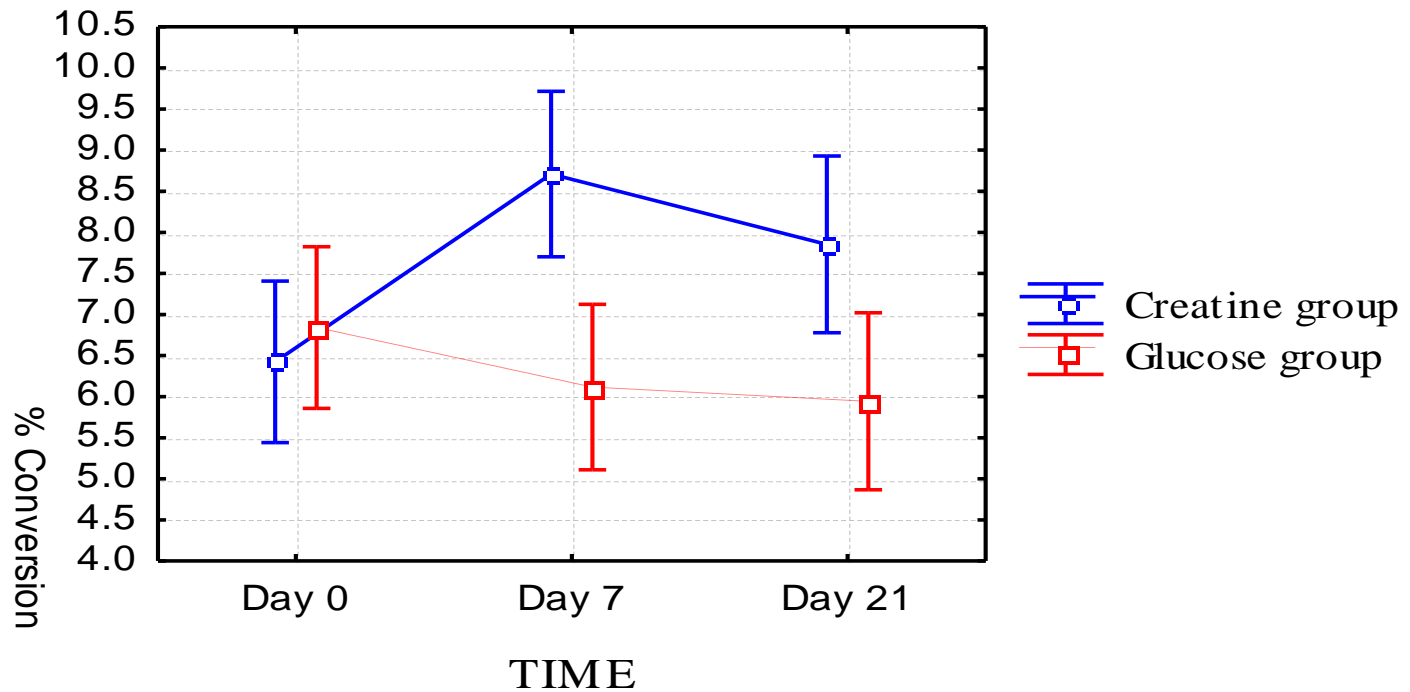
- Creatine monohydrate as a supplement, increases the conversion rate of testosterone to dihydrotestosterone expressed as a % of the available testosterone.



# Creatine supplementation.

% Conversion Testosterone to Dihydrotestosterone

$p < 0.0001$



# What have we got so far?

- Creatine monohydrate supplementation.
- Testosterone.
- Dihydrotestosterone.
- Pluripotent stem cells.
- Satellite cells.
- Androgen receptors.
- Resistance training.



# What are the implications of creatine supplementation.

- Increase Testosterone conversion to DHT.
- Increased levels of the most potent endogenous androgen.
- Increased pluripotent stem cell activity.
- Increased satellite cell production.
- Increased androgen receptors.
- Increased muscle hypertrophy in susceptible individuals.

# What of the ethical/legal issues?

- Is the use of a supplement that increases the endogenous production of a more efficient steroid acceptable?
- Is it acceptable to give a supplement that may cause diseases later in life?
- Could a positive steroid abuse test result follow the use of creatine monohydrate?



# Summary.

- Resistance training increases Testosterone.
- Resistance training increases satellite cells.
- Resistance training increases AR's.
- Creatine supplementation → increases Testosterone conversion to Dihydrotestosterone.
- Increased AR's + increased affinity/molar potency of more Dihydrotestosterone = increased muscle hyperplasia/hypertrophy.

## Take home message

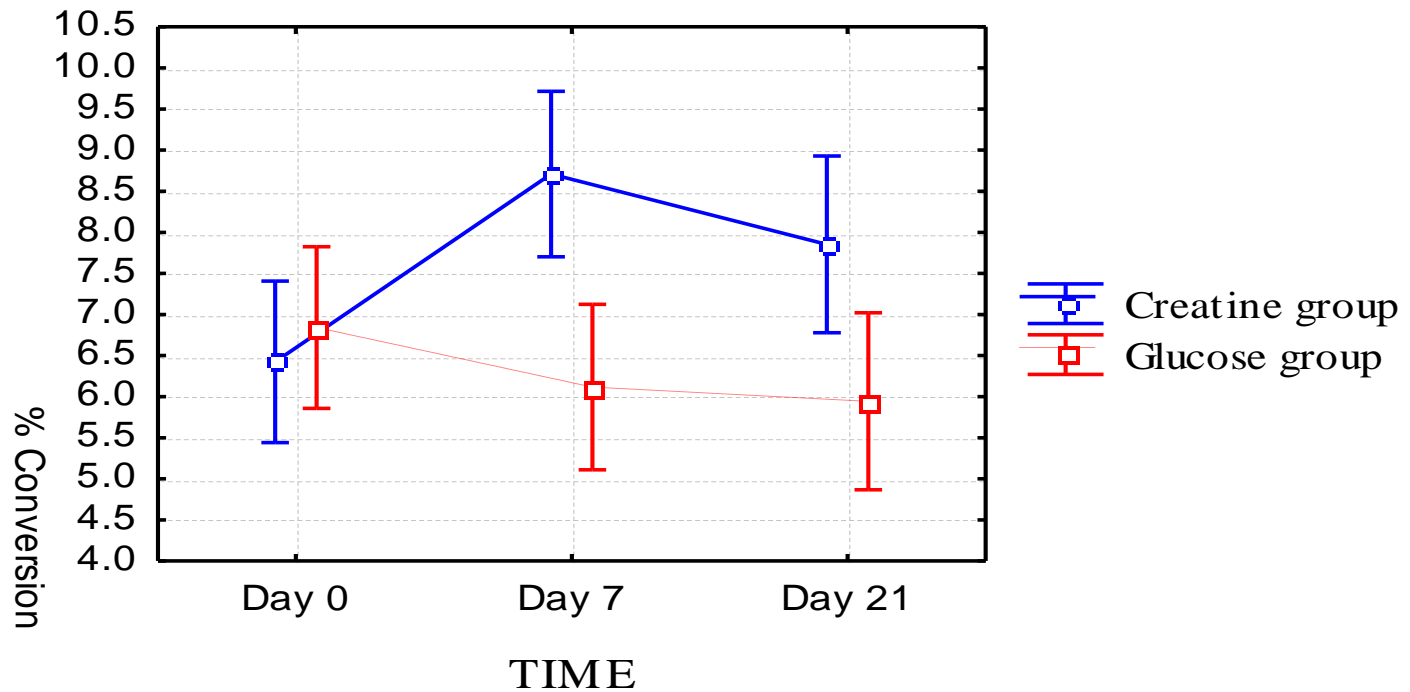
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# Creatine supplementation.

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# Thank you for listening to me

- Feel free to contact me in this regard
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