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CLENBUTEROL & UNIQUE PER-AAS EFFECTS, *REDUX*

TYPE-IIX

6 July 2024 – Presented 11:00 AM EST

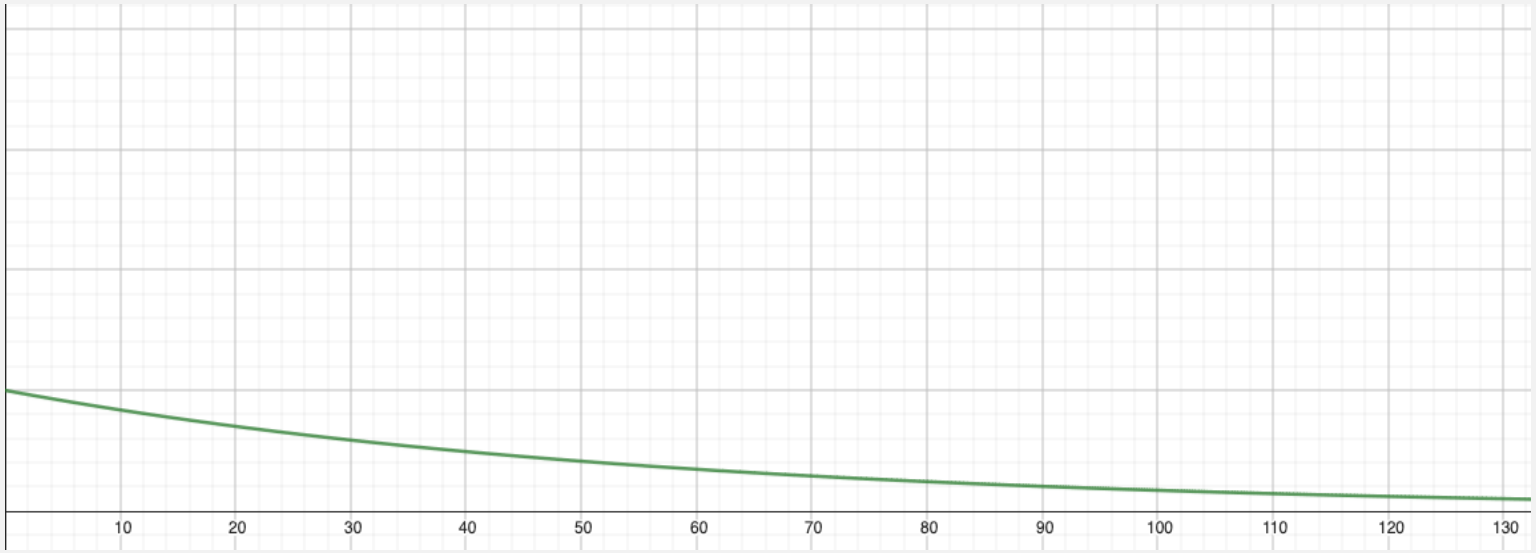
CLEN: INTRODUCTION & BASIC PHARMACOKINETICS

- USED legally in human medicine in a select few countries as a bronchodilator at doses up to 40 µg daily.
- PRACTICALLY, it is used illicitly as well, in agriculture and food production, as a potent partitioning agent to promote growth in cattle and sheep (ruminants).
  - ↓FM (fat mass accrual), &
  - ↑FFM (fat-free, or lean-body, mass accrual)
- BODYBUILDERS therefore use clen for its potently increasing protein accretion and fat removal with little or no change in body weight.
- β-AGONISTS are substances chemically related to epinephrine (adrenaline) ⇒ ↑lipolysis & thermogenesis (↑EE/RMR ⇒ ↑heat dissipation) & ↓lipogenesis.
  - Agonism of the β_2AR stimulates adenylyl cyclase activity (↑ cAMP).
- HIGH oral bioavailability of 70 - 80% and a long half-life of 25-39 hours.
- TACHYPHYLAXIS, or desensitization, is a feature of the β_2AR. This is likely because β_2AR activation and stimulation of downstream effects are a target for phosphorylation and/or because it binds β-arrestin, an accessory protein involved in G protein-coupled receptor (GPCR) desensitization.

CLENBUTEROL VS. ALBUTEROL: BIOLOGICAL ACTIVITY (TIME)

SINGLE-DOSE CLEN IN BLOOD

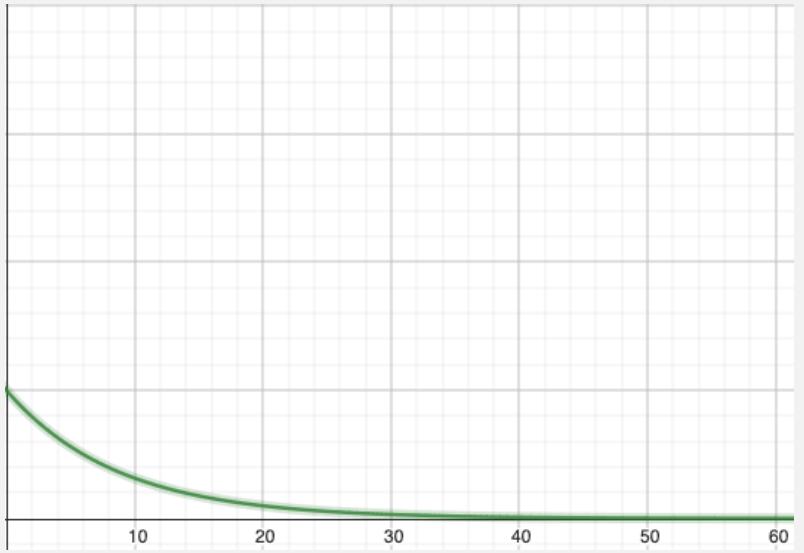
130 H ACTIVITY



$T_{1/2}$ = 39 h

SINGLE-DOSE ALBUTEROL; SALBUTAMOL IN BLOOD

20 H ACTIVITY



$T_{1/2}$ = 6 h

CLASS EFFECTS OF B_2 AGONISTS

BIOCHEMICAL & HEMODYNAMIC

- ↑HR
- ↑BP (systolic) [in combination with ↑HR, indicates sympathomimetic]
- ↓K (serum)
- ↑glucose (serum)
- ↑insulin (serum)
- ↓GH (serum) by ↑SS (hypothalamic)

CARDIOVASCULAR

- ↑HR
- ↑BP (systolic) [in combination with ↑HR, indicates sympathomimetic]
- ↓BP (diastolic)

SIDE EFFECTS OF β_2 AGONISTS

- Electrolyte Disturbance (primarily hypokalemia and hyperglycemia), and ∴
  - Muscle Cramping
- Tachycardia
- Dyskinesia
- Tremor
- Liver Failure
- Muscle Atrophy
- Myocardial Infarction
- Myocardial Reperfusion Injury

CLEN EFFECTS ON BODY COMPOSITION

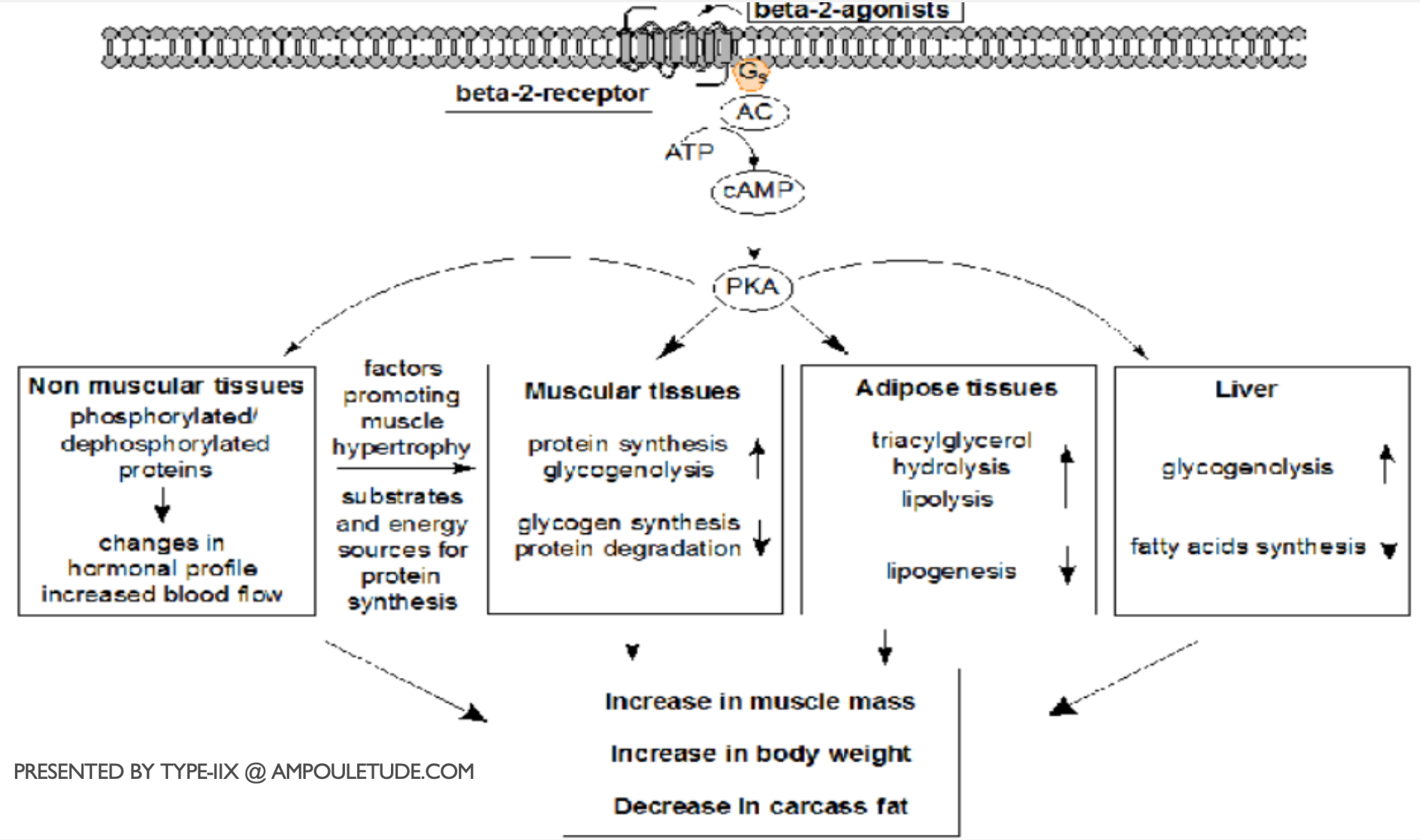
↑ Lean body mass and ↓ fat mass

↑ Skeletal muscle hypertrophy

↑ Lipolysis

↑ RMR

CLEN MECHANISMS OF PARTITIONING (RECOMP)



CLEN MECHANISMS OF HYPERTROPHY

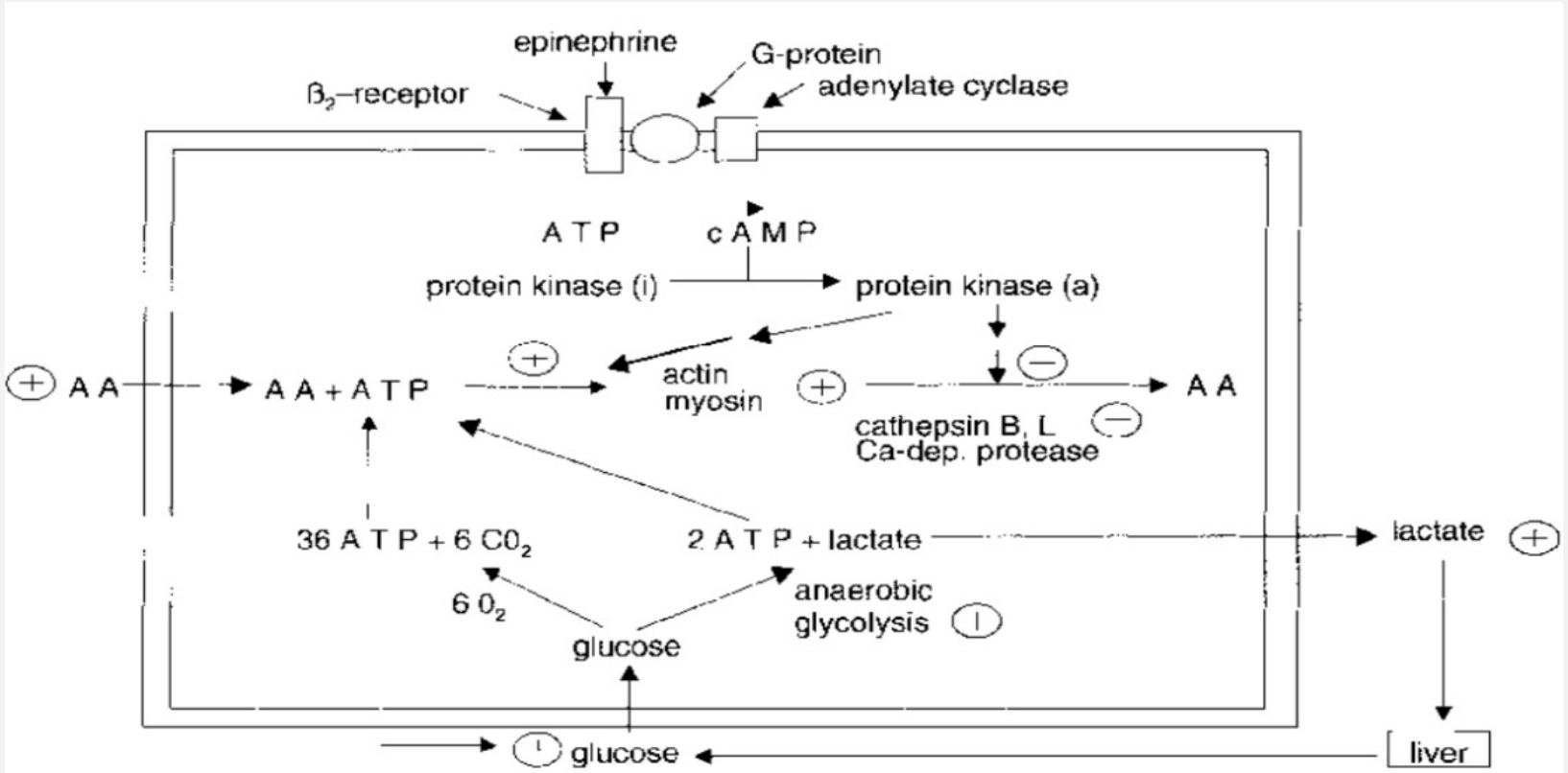


Fig. 4. Cell biology of β_2-agonist mediated anabolism. The signal transduction involves activation of the receptor/adenylate cyclase system, production of the second messenger cAMP, further amplification via an enzyme cascade and activation of protein synthesis (anabolic effect) as well as inhibition of protein degradation (anticatabolic effect). The anaerobic ATP production seems to dominate under the effect of β-agonists. (AA = amino acids).

SUMMARY: CLEN RECOMP EFFECTS

- CHRONIC treatment (e.g., clenbuterol) leads to hypertrophy through pathways (PRIOR 2 SLIDES) that involve the **IGF1-PI3K-Akt-mTOR cascade**.
- **MYOSTATIN inhibition** a la follistatin (FST). After 21 days of a constant dose, Abo et al. observed that myostatin (MSTN) was increased but no change was observed after 7.
- HUMAN skeletal muscle **mTOR phosphorylation** ↑121% (potent activator).
  - "We observed that the increase in lean body mass induced by [B2AR agonist] treatment was 3% when measured by DXA-scan, whereas the increase observed in CSA of muscle fibers was 13–15%."
- AMP activates PKA by dissociating the complex of the regulatory and catalytic subunits. The catalytic subunit of PKA, in turn, phosphorylates different proteins; one, **HSL,** and another, **perilipin**, at the surface of lipid storage. On phosphorylation, HSL translocates from the cytosol to the lipid droplet surface, which becomes accessible to hydrolysis because PKA phosphorylation alleviates the barrier function of perilipin. Finally, triglycerides are hydrolyzed to glycerol and FFAs.
- EIGHTY (80) μg clenbuterol ↑RMR 21% over 3 h (78 kg bodyweight men), fat oxidation ↑39%...
  - ↑plasma concentrations of glucose (+25%), lactate (+87%), insulin (+105%), fatty acids (+129%).

CLEN EFFECTS ON PERFORMANCE STRENGTH, POWER, SPEED

↑ Strength (F): +78 N, 10.26%, E.S. 2.29 for clen (40 µg q.d. as 20 µg b.i.d.) × 6 weeks

↑Power (F/t) [peak & mean]: + 32 ± 8 and 25 ± 9 W, respectively

↑Speed (d/t): Decreased times, corresponding to to a 70 m sprint time and MVC improvement by 5% in competitive athletes and elite cyclists and triathletes, respectively. The % improvement was 3% in sprint and 6% in strength in the respective populations.

CLEN: MECHANISMS OF ENHANCED PERFORMANCE

- SIGNIFICANT interactions (treatment x time) were observed for MVC ($P<0.01$) and peak twitch force ($P<0.01$) between TER and PLA with the intervention… increased MVC by 97 ± 29 N and peak twitch force by 67 ± 14 N compared with PLA. Degree of voluntary activation level, time-to-peak twitch force, and half-relaxation time did not change with the intervention in either group.
- CLENBUTEROL was associated with a decrease in endurance. This paradoxical effect of clenbuterol on strength and endurance… is consistent with animal experimentation that demonstrated a shift from slow to fast twitch fibers and a transition from oxidative to glycolytic metabolism during clenbuterol treatment

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PRACTICAL CLEN CYCLE DESIGN CONSIDERATIONS

Desensitization and Dealing with It

Cardiac Effects and Dealing with Them

Muscle Cramps and Dealing with Them

Effects on GH and Dealing with It

DENSITIZATION AND DEALING WITH IT

- TIME-BOUND – Due to rapid tachyphylaxis:
  - TITRATE dose up on a 5 ± 2 -day cycle, and
  - LIMIT cycle duration to 21 ± 7 days
- ADJUNCT DRUG – KETOTIFEN:
  - KETOTIFEN inhibits cAMP PDE [thereby increasing cAMP activity].
  - KETOTIFEN ↑ cAMP activity [in cardiac cells & lymphocytes] by attenuation of β_2AR downregulation... promotes maintenance of hemodynamic changes – unclear whether the myostatin regulation of β_2AR-induced hypertrophy is altered.
  - UNCLEAR whether the adjuvant use of ketotifen serves to enhance the long-term partitioning ("recomp") effects of clenbuterol. It [ketotifen combination], however, does likely promote more chronic ↑fat loss [by ↑lipolysis, ↓lipogenesis, ↑glycogenolysis, ↓FA synthesis, etc.]). Preservation or loss of the anabolic effects depends on the nature of myostatin cross-talk with β_2AR [i.e., whether downstream from cAMP]).

CARDIAC EFFECTS AND DEALING WITH THEM

- ADJUNCT DRUG – NEBIVOLOL:
  - NEBIVOLOL is a most selective β1 specific antagonist… The mechanism by which clen may induce cardiac necrosis involves catecholamine activation of the β1-adrenergic receptors. To prevent this myotoxic effect, a selective β1 antagonist might be used.

MUSCLE CRAMPS AND DEALING WITH THEM

- NUTRITIONAL SUPPLEMENT – TAURINE:
  - TAURINE alleviates muscle cramps due to electrolyte imbalance (hypokalemia and hyperglycemia mostly) by modulation of intra- and trans- cellular K & Ca in skeletal muscle.
  - Oral administration of taurine in healthy individuals gave a plasma elimination half-life that ranged from 0.7 – 1.4 h. In healthy individuals a clearance rate that ranged from 14 to 34.4 L/h.

DECREASED GH AND DEALING WITH IT

- ADJUNCT DRUG – RhGH [blunt tool] or SS Inhibitor [scalpel]:
  - SINCE CLEN decreases GH secretion by increasing hypothalamic SS secretion, an inhibitor of somatostatin serves a targeted function whereas rhGH a more blunt-force approach to overcoming this GH/IGF-I decrement.
    - CONSIDERATIONS:
      - More profound insulin resistance due to effects on HSL.

QUESTIONS?

TYPE IF YOU MUST

SPEAK IF YOU DARE (*WHY NOT?!*)