The Action of Thyroid Hormones on BMR

Signalling in Health and Disease

Helen Christian HT 2011

The Thyroid gland

- Regulates metabolism in virtually all tissues
- Is of fundamental importance for the development of the CNS in the fetus and newborn
- Thyroid disorders are common – affect 5% of women and 0.5% of men

Developmental effects of T3

- Lungs: stimulates surfactant production and lung maturation (with glucocorticoids)
- CNS: essential for postnatal growth of CNS; stimulates myelin production, axonal growth; cochlear development
- Bone: stimulates linear growth (via chondrocytes); stimulates normal development, maturation, eruption of teeth
Cretinism

- Poor neural development
- Stunted growth
- Can be treated by giving thyroid hormone at birth

Iodide is scarce and insufficient supply is a major health problem in many parts of the world

What is the Basal Metabolic Rate (BMR)?

- The minimum calorific requirement needed to sustain life in a resting individual
- Therefore, the amount of energy your body would burn if you slept all day (24h)
- A major component of total energy expenditure whether resting or working (60-75%)

Thermogenesis

*mechanisms to keep core body temperature constant*

- **Obligatory thermogenesis**
  - the heat loss from regular metabolism

- **Facultative or adaptive thermogenesis**
  - Extra adaptive heat loss to generate more heat eg in cold
  - Mammals – brown adipose tissue BAT
  - 'non-shivering thermogenesis' activated by sympathetic nervous system

BMR is the closest expression of resting obligatory thermogenesis – if BMR increases, heat production increases
How is Basal Metabolic Rate (BMR) measured?

Rarely measured directly, prediction equations used:

General calculation:

\[ \text{BMR (kcals)} = \text{Body weight (in lbs)} \times 10 \text{ kcal/lb} \]

Harris-Benedict equation:

calculation takes into account height and age

WHO 1985

Factors that affect BMR

- **Age**: Aging lowers
- **Height**: Tall, thin people high
- **Growth**: Children and pregnant women high
- **Fasting/starvation**: Lowers
- **Body composition**: Fat lowers, lean mass increases
- **Temperature**: Cold raises

Whole animal indirect calorimetry

\[ \text{O}_2 \text{ consumption and CO}_2 \text{ generation measured} \]

Cellular reactions which make up BMR – obligatory thermogenesis

Sustain ventilation and circulation in minimal state, maintain stable core body temperature

**Increase ATP usage**

- Protein turnover
- Ion movement across the plasma membrane
- Turnover of nucleic acids and lipids

**Reduce efficiency of ATP synthesis**

- Proton leak across mitochondrial inner membrane (uncoupling)
- Increases heat loss, which forces cells to burn more fuel to maintain ATP levels for vital functions
What is uncoupling?

- Proton gradient by respiratory chain is coupled to ATP synthesis
- However, not all of available energy is coupled to ATP synthesis
- ‘Inducible’ proton leak by uncoupling proteins

Effects of T3 on O2 Consumption and Heat Production

- Thyroid hormone controls both obligatory and facultative thermogenesis
- Thyroid hormone increases O2 consumption and heat production in all tissues except brain, spleen and testes
- Clinical evidence for role of thyroid in control of BMR in humans - hyperthyroidism heat intolerance; hypothyroidism cold intolerance

BMR is significantly reduced in TR α + β knockout mice

- Thyroxine increases Na-K-ATPase mRNA
  - Major consumer of ATP
  - Also calcium ATPase unpregulated in SR
Thyroid receptors – genomic actions

- T3 acts on nuclear receptors (Kd 10^{-11}M) which are ‘permanently’ bound to response elements (TREs) in the promotor regions of target genes. Corepressor binding to TR blocks transcription in absence of ligand.
- Heterodimerize with RXR retinoic acid receptors; also TR alpha and beta subtypes.

Rapid ‘non-genomic’ actions of thyroid hormones

- Integrin binds T4 with much higher affinity than T3 – the opposite to nuclear receptors.

Physiological effects:
- Induction of angiogenesis
- Bone resorption
- Brain development and neuronal migration
- Membrane ion pumps

Davis et al 2008

Effects of T3 on lipid and carbohydrate metabolism – obligatory thermogenesis

- Carbohydrate metabolism: potentiates β-glycogenolysis, gluconeogenesis.
- Increases glycogenesis, glucose usage, stimulates gut uptake of glucose.
- Lipid metabolism: stimulates cholesterol breakdown and synthesis; enhances lipolysis.

*Increase ATP consumption in ‘futile’ way to generate heat*

Targets in mitochondria – thyroid hormones reduce efficiency of ATP synthesis

- Mitochondria use 90% of cell oxygen.
- Hepatocytes from hyperthyroid rats have twice the respiration rate of controls.
- Mitochondria from hepatocytes of hyperthyroid animals have increased proton permeability compared to controls – ‘uncoupling’.
Uncoupling proteins

- UCP1: mitochondria in Brown Adipose Tissue (BAT) adipocytes
- UCP2: BAT, cardiac muscle, white adipose, kidney, lung, immune system
- UCP3: BAT and skeletal muscle

Stimulation of uncoupling by thyroid hormones

- Two theories
  - Thyroid hormones act directly at the membrane to make membranes more rigid, change in phospholipid composition – now disregarded
  - Transcriptional upregulation of uncoupling proteins?

T3 stimulates UCP2 and UCP3 expression in WAT and skeletal muscle

However T3 induced thermogenesis intact in UCP3 KO mouse

T3 thermogenic response intact
Compensation in KO?

Gong et al 2000, J Biol Chem
Facultative thermogenesis: T3 modulates adrenergic sensitivity of adipose tissue

- Tissues in hypothyroid animals have reduced responsiveness to adrenergic stimulation
- T3 induces \( \beta_3 \) receptor expression
- Noradrenaline induces T3 production from T4 in adipocytes via type 2 deiodinase activation

Effect of TR Ablation on Adrenergic Sensitivity of Freshly Isolated Brown Fat Cells

Ten fold less sensitive to noradrenaline

BAT thermogenic response is initiated by Nor A but need T3 for full effect

Golozoubova et al, 2004

Types of deiodinase

- Type 1 - provides T3 to plasma
  Location - liver, kidney
- Type 2 – provides intracellular T3
  Location - brain, pituitary, adipose
- Type 3 - inactivates T3 and T4
  Location - brain, placenta

The type 2 iodothyronine deiodinase is essential for adaptive thermogenesis in brown adipose tissue

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Mice show cold intolerance yet plasma T3 normal is – local generation therefore very important
Bile acid signalling – signal of food availability that bridges nutrition with metabolism

Bile acids also enters circulation

Bile activates deiodinase type 2 in brown fat

Watanabe et al Nature 439 2006

Bile secreted after meal to promote fat absorption

Oxygen consumption increases, effect not seen in DIO2 KO mouse

Would you use thyroxine as a way to lower weight in obese patients?

Discuss with your neighbour and decide yes or no and why

To support thermogenesis need energy –T3
Stimulates Food Intake via the Hypothalamic Ventromedial Nucleus

about 5–10% of hyperthyroid individuals have a sufficiently increased appetite to gain weight despite the catabolic thyrotoxic process, suggesting that thyroid hormones may directly stimulate feeding

Kong et al 2004

Thermogenesis depends on oxygen supply to tissues - effects of T3 on the cardiovascular system

- increases cardiac output, rate, force, systolic blood pressure
- diastolic blood pressure falls because of vasodilatation
- ’bounding pulse’ in hyperthyroidism, weak pulse in hypothyroidism
- Increases transcription of β receptors, Ca²⁺ ATPase

Marrif et al 2005
Is there seasonal variation in BMR in humans?

Tibetan Nomads, live at extremes of temperature and altitude (5000m)
- Marked seasonal variation in food intake
- Few calories and no meat in Summer
- Winter calorific intake increases 50-250%, lots of meat

Results
- BMR in both seasons within normal range
- No evidence for lower Summer BMR to compensate for low calorie intake
- However, body fat accumulated during the Winter

Does thyroid activity increase in response to cold in man?

Military recruits acclimatized to cold over 4 weeks
- Joy et al 1963
  Increased thermogenic responses to noradrenaline
- Skreslet et al 1968
  Increased thermal insulation by body fat

Thyroid hormones and treatment of obesity

- Thyroid hormones have a long history in the treatment of obesity
- However, no longer used due to side effects:
  - Increased heart weight
  - Tachycardia, atrial arrhythmias
  - Thyroid atrophy
  - Loss of lean body mass
  - Bone loss

Summary

- Thyroid hormones important for many physiological processes
- Primary regulator of basal metabolic rate but little is understood regarding exact mechanisms of control
- Therapeutic uses of thyroxine in obesity limited by side effects