Lecture 1A

Systems biology: the systematic study of complex interactions in biological systems

- Better understand entirety of the complexity of processes that happen in biological system
- Perturb them (biologically, genetically, chemically)
- Monitor gene, protein, informational pathway responses
- Purpose to predict outcomes or responses in a living system

Emergent properties: properties of an entire system (or organism) that are not necessarily evident from examining individual components

Bioinformatics: formulating mathematical models that describe the structure of the system and its response to the individual perturbations

Genomics: study of organism's complete set of DNA

Proteomics: study of the set of all proteins produced in a biological unit

Metabolomics: study of metabolites within a given unit

Reduction	Integration
• Isolated models (molecules, cells, organs, tissues) • Exquisite control over experimental conditions • Can elucidate mechanisms	• Integrated whole-body or organism • Less control over variables • Less mechanistic • "Real world"

Insulin (isolated experiments)

- Promotes glucose uptake into muscle
- Slow down release of glucose by the liver
- Slow down fat breakdown, etc.

Ghrelin "hunger hormone"

- Isolated fat cells
    - Slows down the breakdown of fat (lipolysis)
- Integrated in rodent
    - Stimulates growth hormone release, stimulates lipolysis
    - Overrides reduction in fat breakdown

What limits maximal oxygen uptake?

- Single leg extensions
    - VO2 limited by muscle mitochondrial content
    - Does not have big hormonal, blood flow, or systemic changes
- Whole body exercise
    - VO2 limited by cardiac output (heart)

Oxidative Damage

- Constant production of reactive oxygen species (ROS)
- React with things in cell (DNA, proteins, lipids) and damage them
- Promotes aging and disease
- Antioxidants like blueberries, grapes, Vitamin C
- YES → antioxidants protect the cell from damaging effects
- NO → certain amount of ROS is necessary (ie. apoptosis of damaged cells); ROS are natural signal involved in adaptation of stressed tissues like muscle, where antioxidants can block mitochondrial adaptions to exercise training
- Study when given large doses of Vitamin C
    - Training induced increase in VO2 max is blunted; training-improved endurance impaired
    - PGC-1 (synthesis of mitochondria) scientifically decreases

Lecture 1B

Single nucleotide polymorphisms (SNPs): single nucleotide base mutations/substitutions that alters function or (more likely) amount of protein

- Most occur in non-coding regions, not part of gene that codes of protein; promoter regions, response elements

Epigenetics: DNA methylation/demethylation and histone modification which alters expression of genes/protein

Nutrigenomics: nutrients can alter gene expression; ie. fatty acids activate PPARs, which in turn can alter expression of certain genes like hepatic gluconeogenesis

Control and Communication Network (coordinate functions of the person- networking)

1. Central nervous system – brain and spinal cord
2. Peripheral nervous system – somatic (voluntary) and autonomic (involuntary) nervous system
3. Endocrine system – endocrine tissues and exocrine glands, hormones
4. Support and defense system – support, movement, maintenance, repair, adaption, defenses (non-specific and specific)

- Control and coordinates the function of all physiological systems and individual organs, including itself
- Distributed throughout the entire body; four major components of CCN are not separable
- Each component has multiple functions and the network has redundancy
- Information flow within in via chemical-based, cell-cell communication
- Personality is an emergent property of the CCN
- Integrator of inputs to health, disease and aging – genetics environment and lifestyle
- Integrator of output to the seven dimensions of health (spiritual, physical, mental, social, emotional, environmental, occupational)
- Aging/disease result from compromised/diminished/altered function/structure

- P4 Medicine- personalized, predictive, preventive, participatory
    - System Biology approach to health
    - “individual” approach; many things we cannot reliably predict

Lecture 2

Experimental Models

1. Simulations with mathematic models/computer (in silico)
2. In vitro and ex-vivo models (cell culture, isolated tissues/organs)
3. Animals models
4. Human subjects

- C. Elegans (nematode)
    - 40% genetic homology to human
    - Short life cycle (~3 days)
    - Self fertilizes
    - Can be frozen/thawed, and remains viable
    - Transparent- facilities study of cell differentiation
    - Embryonic metabolism- turning “on” and “off” of genes and pathways
    - Florescent tag can follow digestion of nutrient, synthesis of proteins, cholesterol, etc.
- Drosophila Melanogaster (fruit fly)
    - 65% genetic homology to human
    - Life cycle and development are sensitive to environmental conditions
    - Neuropharmacology research- study effect of drugs/alcohol
- Rats
    - Social, intelligent
    - Study lifestyle effects on metabolism (diets, exercise, drugs)
    - More severe approach than with human studies
    - Not good model for human infants (nutrition, metabolism)
    - Genetically modified, but not as common as mice
- Mice
    - Ease of applying recombinant DNA technology
    - Test importance of single protein
    - Compensatory mechanism
    - Study lifestyle effects on metabolism
    - Cannot assume similar results as rats/other rodents

Low glucose infusion rate: insulin is not working very well, not insulin sensitive/responsive

High glucose infusion rate: Very responsive to insulin

Deficient in leptin: low glucose infusion rate; insulin resistant; ability of insulin to suppress liver’s production of glucose is not very good (keeps producing glucose)

Leptin therapy- the ability of insulin to suppress glucose double (is better)

Lipoatrophy: body does not produce fat cells, is very thin; fat get deposited into organs/tissues instead

- Swine (pigs)
    - Piglets are best non-primate model for human infant development and metabolism
    - Study organ transplants (xenografts)
- Primates (monkeys)
    - Closest model to represent human
    - Ethics and cost
    - Little primate research in Canada; more in USA
    - Human pathologies (AIDS), transplantation, drug abuse, toxicology

Non-interventional Studies (non-clinical)

- No treatment given
- Cannot prove cause-and-effect; only predicts associations/correlations
- Commonly epidemiological studies

Interventional Studies (clinical)

- Investigation involving human participants that evaluates the effects of 1+ health-related interventions on health outcomes
- Medical treatment, control substance/placebo
    - Predict cause-and-effect
    - Double-blind clinical trials → gold standard
- Can be interventional but not clinical; clinical must be health-related

Testing New Drug (~10 years)

1. Test experimental drug on small group of people; drug's safety (dosage range, side effects)
2. Larger group (100+) to gather data on effectiveness to treat, safety, and best dose
3. Larger group (1000+) to ensure effectiveness, monitor side effects, compare to commonly used treatments
4. Trials take place after drug is approved and on the market; information gather on best way to use and long-term benefits/risks

Cochrane Collaboration: generates systematic review of primary literature using human clinical trials

New Dimensions in Medical and Healthcare Practice

1. Evolutionary medicine
    - Responses adapted/developed through evolution
    - Paleolithic diet to mimic early diets (healthy?)
    - Fight or flight response- always activated with no follow-through ("stress kills")
2. Collective medicine- Eco Health and One Health/One World
    - Promote/improve/defend the health and well-being of all species