

BIOM30001

Frontiers in Biomedicine



H1 Comprehensive Subject Notes

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Metabolic Syndrome

Introduction to metabolic syndrome

What is Metabolic Syndrome?

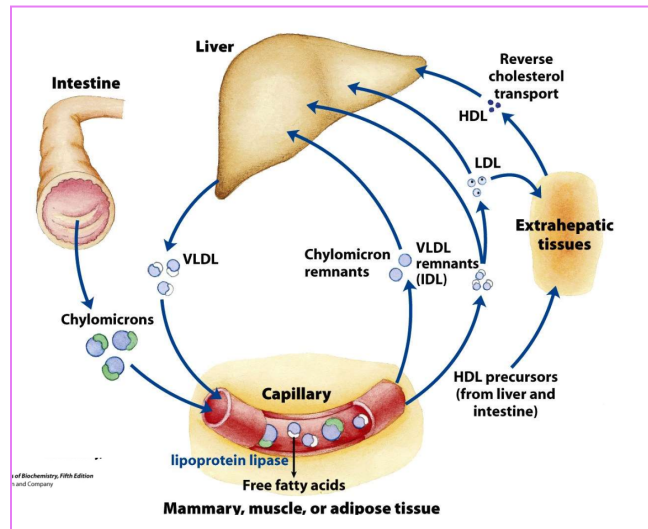
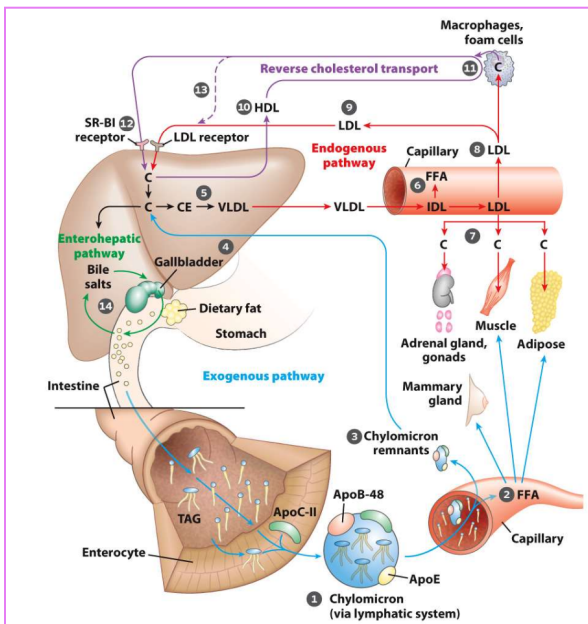
- A collection of interconnected factors that cause a direct risk in cardiovascular disease and type 2 diabetes mellitus. These risk factors co-exist and occur together more often than by chance alone
- RISK FACTORS include:
 - Raised blood pressure
 - Central obesity
 - Dyslipidemia (raised TGs and lowered HDLs)
 - Raised fasting glucose

Significance of the features of metabolic syndrome

- **Raised blood pressure**
 - Increased BP (hypertension) inflicts damage onto the endothelial wall of arteries which can lead to a cascade of events including weakening and formation of atherosclerosis which ultimately prevents blood flow to the heart inflicting cardiac stress.
 - Obesity increases the workload on the heart and blood vessels, physically increasing BP, and also releasing hormones such as aldosterone, which contributes to increased BP via RAAS.
- **Central obesity**
 - Categorised by a large waistline and measurements vary based on ethnic groups
 - If BMI is over 30, central obesity can be assumed
 - **Visceral fat** is stored in the abdominal region, known as *hidden fat*
 - **Visceral fat** -> increased insulin resistance, high TGs, inflammation, more cytokine levels
 - Secrete **less leptin** and are associated with **higher levels of cortisol**
- **High triglycerides**
 - Excess triglycerides lead to release of fatty acids into the bloodstream
 - Increase risk of heart disease and stroke
 - Coincide with low HDL
 - Increase risks of fat accumulation in pancreas -> pancreatitis
 - Triglycerides and cholesterol circulate in the blood (lead to atherosclerosis, embolism)
- **Reduced HDL**
 - Cholesterol is transported across the body via fatty acid esterification to make it more hydrophobic so it can be incorporated into protein/lipid composites and lipoproteins such as VLDL for delivery to tissues. (cholesterol is amphiphilic)
 - Dangers of dyslipidemia - atherosclerosis!
 - Obesity reduces HDL levels; insulin resistance reduces HDL production by liver
- **Elevated fasting glucose**
 - Measure via random plasma glucose test, fasting plasma glucose test, oral glucose tolerance
 - **Due to insulin resistance, when cells fail to respond effectively to insulin resulting in high blood glucose.**

- **Reverse cholesterol transport**

- **Lipoprotein: HDL**
- **Picks up excess cholesterol from tissues and transports it back to liver**
- Protects against cholesterol buildup and atherosclerosis.



Formation of atherosclerotic plaques with lipoprotein and lipid transport

- LDL is a lipoprotein responsible for transporting cholesterol from the liver to tissues (to the muscle, adrenal glands and adipose) through the bloodstream.
- When **LDL levels are too high, they can accumulate in blood vessel causing damage** and weakening endothelial lining -> cytokines release signals to get help -> macrophages ingest cholesterol in attempt to clean up however they tend to burst -> accumulation of **LDL and foam cells** forms a atherosclerotic plaque -> clotting factors accumulate -> formation of a thrombus -> narrowing and occlusion of blood vessel by embolism -> cardiovascular risks -> MI (or stroke).

Therapeutics to lower cholesterol

- **Statins** competitively inhibit HMG-CoA reductase thus inhibiting the production of cholesterol.
- HMG-CoA reductase is the rate limiting enzyme in cholesterol synthesis

Social and political view of Metabolic Syndrome

Incidence, prevalence and risk factor

- **Incidence** - rate at which new cases occur in a population
- **Prevalence** - proportion of a population that are cases
- **Risk factor** - a factor that increases chances of disease occurring

Feeding and weight control

Describe how peripheral satiety and adiposity signals regulate body weight

- **Insulin**
 - **Regulates blood glucose and signals satiety**
 - Secreted by the pancreas
 - Acts on the hypothalamus to reduce appetite and increase energy expenditure
 - *Lower insulin levels associated with more hunger and weight gain*
- **Leptin**
 - **Signals satiety by signalling to the brain about energy storage**
 - Secreted from white adipose tissue (fat cells)
 - Signals brain to decrease food intake when there are sufficient energy stores (lots of fat)
 - *Low leptin increases appetite*
- **Ghrelin**
 - **'Hunger hormone' - signals hunger**
 - Released from the stomach signifying hunger
 - Receptors (GSHR-1a) are located in the hypothalamus

Explain how hypothalamic neuropeptides are involved in regulating body weight.

- In the hypothalamus:
 - **Neuropeptide Y (NPY)** and **agouti-related peptide (AgRP)** increase food intake.
 - **alpha-MSH** inhibits appetite and increases energy expenditure.
- **Neuropeptide Y (NPY)**
 - Produced in the arcuate nucleus
 - Stimulates hunger
 - Increases food intake.
- **AgRP**
 - Produced alongside NPY in the arcuate nucleus
 - Increases food intake and decreases energy expenditure
 - Works as an antagonist in the MC4 receptor, thus promoting hunger
- **alpha-MSH**
 - Derived from proopiomelanocortin (POMC) neurons in the hypothalamus
 - Binds to the MC4R receptor in the paraventricular nucleus inhibiting appetite, thus decreased food intake
 - *Mutation in POMC or MCR4 genes result in obesity.*
- **Ghrelin increases NPY and AgRP synthesis and release, increasing food intake via orexigenic path.**
- **Leptin decreases NPY and AgRP, increasing POMC and thus release of alpha-MSH, decreasing food intake via anorexigenic path.**

COPD medications

- **Bronchodilators**

- **Beta-agonists**

- **MOA**

- Activates beta-2 on airway epithelium -> stimulates adenylate cyclase which converts ATP to cAMP -> increases PKA and decreases intracellular Ca^{2+} -> inhibits MLC-K -> no actin-myosin crossbridge -> no contraction -> **bronchodilation**

- **Short-acting beta agonist (LABA)**

- Reliever
 - E.g. **salbutamol**
 - Counteracts actions of ACh; M3 receptors increase Ca^{2+} and induce bronchoconstriction

- **Long-acting beta agonist (LABA)**

- Preventer (used for prophylaxis)
 - E.g. **salmeterol, formoterol**

- **IMPORTANT:** Frequent use associated with poor outcomes due to beta-2 adrenoceptor downregulation decreasing bronchodilator response. Therefore, **beta 2-agonists must be combined with ICS!**

- **Long-acting muscarinic antagonist (LAMA)**

- *Controller*

- block muscarinic receptors, preventing muscle contraction in airways and facilitating relaxation

- **MOA**

- Activates G_q -> stimulates phospholipase C -> increases IP3 and DAG
 - IP3 (inositol triphosphate) -> increases Ca^{2+}
 - DAG (diacylglycerol) -> increases PKC
 - Ca^{2+} and PKC -> **bronchodilation**

- e.g. **vilanterol**, indacaterol, olodaterol, **formoterol**, salmeterol

- **Steroids**

- *preventers*

- Mimics the effects of endogenous cortisol
 - ICS must be lipophilic to penetrate cell membrane
 - e.g. **beclomethasone, budesonide, fluticasone, mometasone**

- **MOA**

- ICS binds to glucocorticoid receptors in the cytoplasm
 - Glucocorticoid-receptor complex dimerises and is translocated into the nucleus
 - Inside the nucleus the activated complex interacts with DNA to modulate gene transcription

Multiple Usages of the Term iatrogenesis

- **Clinical iatrogenesis**

- Refers to harm caused directly by medical interventions, such as side effects from medications (e.g., weight gain from antipsychotics).

Drugs in mental health

Describe the main neurotransmitters, pathways and brain regions involved in the development of dependence on drugs that act on the CNS1.

- **Main neurotransmitters**

- **Dopamine**

- Brain's reward systems - involved in the reinforcement of behaviors associated with pleasure and reward.
 - Many **drugs of abuse**, such as **cocaine**, **amphetamines**, and **opioids**, increase dopamine levels in the brain, particularly in the mesolimbic pathway, leading to feelings of euphoria and reinforcing drug-seeking behavior.

- **Serotonin**

- Involved in mood regulation, impulse control, and modulation of anxiety and depression.
 - **Drugs** like **MDMA** (Ecstasy) increase serotonin levels, affecting mood and emotional well-being, which can lead to repeated use and dependence.

- **Gamma-Aminobutyric Acid (GABA)**

- GABA is the **primary inhibitory neurotransmitter** in the brain, playing a crucial role in reducing neuronal excitability.
 - **Benzodiazepines** and **alcohol** enhance GABAergic activity, leading to sedative effects. Chronic use can lead to tolerance and dependence as the brain adapts to the increased inhibitory signals.

- **Glutamate**

- Glutamate is the **main excitatory neurotransmitter** in the CNS, essential for synaptic plasticity and learning.
 - Chronic drug use can disrupt glutamatergic signalling, contributing to cravings and withdrawal symptoms during abstinence.

- **Noradrenaline**

- NA is involved in the body's stress response and can influence arousal and alertness.
 - Stimulants like **cocaine** and **methamphetamine** increase NA release, which can lead to heightened arousal and potential dependence.

- **Key Neural Pathways**

- **Mesolimbic Pathway**

- Projects from the **ventral tegmental area (VTA) to the nucleus accumbens (NAc)** and is central to the reward system.
 - Mediates the rewarding effects of drugs and is involved in reinforcement learning, making it a crucial pathway for understanding addiction.

- **Mesocortical Pathway**

- Connects the **VTA to the prefrontal cortex (PFC)**.
 - Involved in decision-making, impulse control, and emotional regulation. Dysregulation in this pathway can lead to impaired judgement and increased risk of dependence.