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18/MHS01/385

Medicine & Surgery

Biochemistry assignment.

Question

1. What do you understand by primary or simple obesity?
2. How does congenital syndrome and drug therapy affect obesity?
3. Outline the aetiology of cancer and its molecular basis.
4. Simple or primary obesity is characterized by a normal or increased growth rate with an acceleration of bone age maturation. Obesity can be classified as primary since the adioposopathy determines the dysregulation of the metabolic pathways. This adioposopathy is sustained by adipocyte hypertrophy, visceral adiposity and or ectopic fat deposition and secretion of hormones like leptin. Metabolic diseases most associated with primary obesity contribute to atherosclerosis, hypertension, dyslipidemia, diabetes type II etc.
5. Drug therapy which is also called pharmacotherapy is a general term for using medication to treat diseases. Drug therapy affects obesity by helping obese people through the availability of some certain drugs to reduce weight via inhibiting appetite enhancing hormones.

 APPETITE SUPPRESSANTS

Various pharmacologic agents, referred to as anorectic drugs, are used as adjuncts to behavioral therapy in weight reduction programs. The two classes of anorectic drugs currently available are the noradrenergic and the serotonergic agents.

Noradrenergic Agents. Noradrenergic drugs affect weight loss through action in the appetite center. Phenylpropanolamine (Dexatrim), a sympathomimetic drug and a synthetic derivative of ephedrine, in studies lasting 14 weeks, the subjects who took phenylpropanolamine had a greater weight loss than those who took placebo. When phenylpropanolamine is used in the treatment of obesity, the manufacturers recommend physician supervision if patients are also being treated for high blood pressure, depression or anxiety disorder, or if they have diabetes, heart disease or thyroid disease.

*Phentermine (Ionamin)* is structurally similar to amphetamine and modulates noradrenergic neurotransmission to decrease appetite; however, it has little or no effect on dopaminergic neurotransmission. The use of phentermine as a single agent is usually limited by an intolerance to its stimulatory activity. Phentermine was previously used in combination with fenfluramine (Pondimin) to improve weight loss and counteract the adverse effects of use of phentermine. Because of the withdrawal of fenfluramine from the market, phentermine is now used as a single weight-loss agent. Phentermine is labeled for the management of exogenous obesity as a short-term (i.e., a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The most common adverse effects of phentermine include headache, insomnia, nervousness and irritability. Palpitations, tachycardia and elevations in blood pressure may also occur. Phentermine should not be taken by persons with hyperthyroidism, glaucoma, agitated states, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension or a history of drug abuse.

Serotonergic Agents. The serotonergic drugs partially inhibit the reuptake of serotonin and release serotonin into the synaptic cleft, thus acting on the hypothalamus to decrease satiety.

*Fluoxetine (Prozac)* is a highly selective serotonin reuptake inhibitor (SSRI) that has been studied in the treatment of obesity. Fluoxetine may increase energy expenditure by raising basal body temperature; however, weight loss has not been consistent among subjects in clinical trials.

 *Sibutramine (Meridia)* is an adrenergic/serotonergic agent recently labeled by the FDA for use in the management of obesity. Sibutramine and its metabolite inhibit monoamine uptake, suppressing appetite in a fashion similar to SSRIs. Sibutramine may also stimulate thermogenesis by activating the beta3-system in brown adipose tissue. Sibutramine was found to cause weight loss 1 to 2 kg (2.2 to 4.4 lb) in healthy and depressed patient. In a continued, open-label, 96-week extension study, weight was regained even in subjects taking high-dose sibutramine. Sibutramine is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. It is recommended for obese patients with an initial BMI of greater than 30 kg per m2, or greater than 27 kg per m2 in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia). The recommended starting dosage of sibutramine is 10 mg administered once daily with or without food. If there is inadequate weight loss after four weeks, the dosage may be titrated to 15 mg administered once daily.

DIGESTIVE INHIBITORS

Another strategy in the treatment of obesity is to use digestive inhibitors that interfere with the breakdown, digestion and absorption of dietary fat in the gastrointestinal tract. A reduction in fat is recommended in most weight loss diets; however, patient compliance with these diets is generally poor. Therefore, digestive inhibitors may have a role in creating the negative energy balance necessary for subsequent weight loss. Gastric and pancreatic lipases aid in the digestion of dietary triglycerides by forming them into free fatty acids that are then absorbed at the brush border of the small intestine. Inhibition of these enzymes leads to inhibition of the digestion of dietary triglycerides and decreased cholesterol absorption, and may decrease absorption of lipid-soluble vitamins (A, D, E and K).24 Orlistat (Xenical), the first lipase inhibitor labeled by the FDA for treatment of obesity, is a potent and irreversible inhibitor of gastric and pancreatic lipases, preventing the absorption of about 30 percent of dietary fat. Orlistat is indicated for use in patients with a BMI of at least 30 kg per m2 or in patients with hypertension, diabetes or dyslipidemia who have a BMI of greater than 27 kg per m2. Based on orlistat's mechanism of action, side effects would be more significant in patients eating a high-fat diet. Gastrointestinal side effects included flatus with discharge, oily spotting and oily stool, fecal urgency, fecal incontinence and abdominal pain.

HORMONAL MANIPULATION

The gastrointestinal tract and central nervous system contain several peptides and hormones that regulate feeding behavior. For example, cholecystokinin and serotonin act to decrease appetite and food intake. Conversely, neuropeptide Y increases food intake and decreases energy expenditure. Leptin may limit food intake, decrease plasma insulin and increase energy expenditure. Therefore, agonists and antagonists of these hormones and peptides are currently under investigation for the treatment of obesity.

* Congenital obesity is the excessive accumulation and storage of fat in the body that is present during infancy and/or childhood. Obesity may be diagnosed as an isolated clinical finding or as a part of syndromic findings. Monogenic forms of childhood obesity are very rare. Mutations in only a few genes controlling appetite and metabolism are known to cause the development of severe obesity in early childhood.

Syndromic causes of congenital and early-onset obesity include:

Albright hereditary osteodystrophy

Alstrom syndrome

Bardet-Biedl syndrome

Borjeson-Forssman-Lehmann syndrome

Cohen syndrome

Schaaf-Yang syndrome (also called Prader-Willi-like syndrome)

Leptin deficiency

Leptin receptor deficiency

MC4R (melanocortin 4 receptor) deficiency

 Congenital leptin deficiency is a condition that causes severe obesity beginning in the first few months of life. Affected individuals are of normal weight at birth, but they are constantly hungry and quickly gain weight. Without treatment, the extreme hunger continues and leads to chronic excessive eating (hyperphagia) and obesity. Beginning in early childhood, affected individuals develop abnormal eating behaviors such as fighting with other children over food, hoarding food, and eating in secret. People with congenital leptin deficiency also have hypogonadotropic hypogonadism, which is a condition caused by reduced production of hormones that direct sexual development. Without treatment, affected individuals experience delayed puberty or do not go through puberty, and may be unable to conceive children (infertile). Congenital leptin deficiency is caused by mutations in the LEP gene. This gene provides instructions for making a hormone called leptin, which is involved in the regulation of body weight. Normally, the body's fat cells release leptin in proportion to their size. As fat accumulates in cells, more leptin is produced. This rise in leptin indicates that fat stores are increasing. Leptin attaches (binds) to and activates a protein called the leptin receptor, fitting into the receptor like a key into a lock. The leptin receptor protein is found on the surface of cells in many organs and tissues of the body including a part of the brain called the hypothalamus. The hypothalamus controls hunger and thirst as well as other functions such as sleep, moods, and body temperature. It also regulates the release of many hormones that have functions throughout the body. In the hypothalamus, the binding of leptin to its receptor triggers a series of chemical signals that affect hunger and help produce a feeling of fullness (satiety). LEP gene mutations that cause congenital leptin deficiency lead to an absence of leptin. As a result, the signaling that triggers feelings of satiety do not occur, leading to the excessive hunger and weight gain associated with this disorder. This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

1. Cancer is a disease caused by genetic changes leading to uncontrolled cell growth and tumor formation. The basic cause of sporadic (non-familial) cancers is DNA damage and genomic instability. A minority of cancers are due to inherited genetic mutations. Most cancers are related to environmental, lifestyle, or behavioral exposures. Cancer is generally not contagious in humans, though it can be caused by oncoviruses and cancer bacteria. The term "environmental", as used by cancer researchers, refers to everything outside the body that interacts with humans. The environment is not limited to the biophysical environment (e.g. exposure to factors such as air pollution or sunlight), but also includes lifestyle and behavioral factors. Common environmental factors that contribute to cancer death include exposure to different chemical and physical agents (tobacco use accounts for 25–30% of cancer deaths), environmental pollutants, diet and obesity (30–35%), infections (15–20%), and radiation (both ionizing and non-ionizing, up to 10%).These factors act, at least partly, by altering the function of genes within cells. Typically, many such genetic changes are required before cancer develops. Aging has been repeatedly and consistently regarded as an important aspect to consider when evaluating the risk factors for the development of particular cancers. Many molecular and cellular changes involved in the development of cancer accumulate during the aging process and eventually manifest as cancer.

Many of the cancer syndrome cases are caused by mutations in tumor suppressor genes that regulate cell growth. Other common mutations alter the function of DNA repair genes, oncogenes and genes involved in the production of blood vessels. Certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer. Some of the inherited genetic disorders that can cause colorectal cancer include familial adenomatous polyposis and hereditary non-polyposis colon cancer; however, these represent less than 5% of colon cancer cases.

The incidence of lung cancer is highly correlated with smoking. Tobacco smoking is associated with many forms of cancer, and causes 80% of lung cancer. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Tobacco is responsible for about one in three of all cancer deaths in the developed world, and about one in five worldwide.

Alcohol is an example of a chemical carcinogen. The World Health Organization has classified alcohol as a Group 1 carcinogen. In particular, alcohol use has been shown to increase the risk of developing cancers of the mouth, esophagus, pharynx, larynx, stomach, liver, ovaries, and colon. The main mechanism of cancer development involves increased exposure to acetaldehyde, a carcinogen and breakdown product of ethanol. Other mechanisms have been proposed, including alcohol-related nutritional deficiencies, changes in DNA methylation, and induction of oxidative stress in tissues.

HPV is the most common virus that infects the reproductive tract. Infection can lead to the development of cervical cancer in women. Viral infection is a major risk factor for cervical and liver cancer. A virus that can cause cancer is called an oncovirus. These include human papillomavirus (cervical carcinoma), Epstein–Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1 (T-cell leukemias).

Certain bacterial infections also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma. The mechanism by which H. pylori causes cancer may involve chronic inflammation or the direct action of some of the bacteria's virulence factors. Parasitic infections strongly associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini and Clonorchis sinensis (cholangiocarcinoma). Inflammation triggered by the worm's eggs appears to be the cancer-causing mechanism. Certain parasitic infections can also increase the presence of carcinogenic compounds in the body, leading to the development of cancers.

Up to 10% of invasive cancers are related to radiation exposure, including both non-ionizing radiation and ionizing radiation. Unlike chemical or physical triggers for cancer, ionizing radiation hits molecules within cells randomly. If it happens to strike a chromosome, it can break the chromosome, result in an abnormal number of chromosomes, inactivate one or more genes in the part of the chromosome that it hit, delete parts of the DNA sequence, cause chromosome translocations, or cause other types of chromosome abnormalities. Major damage normally results in the cell dying, but smaller damage may leave a stable, partly functional cell that may be capable of proliferating and developing into cancer, especially if tumor suppressor genes were damaged by the radiation. Three independent stages appear to be involved in the creation of cancer with ionizing radiation: morphological changes to the cell, acquiring cellular immortality (losing normal, life-limiting cell regulatory processes), and adaptations that favor formation of a tumor. Even if the radiation particle does not strike the DNA directly, it triggers responses from cells that indirectly increase the likelihood of mutation. Higher-energy radiation, including ultraviolet radiation (present in sunlight), x-rays, and gamma radiation, generally is carcinogenic, if received in sufficient doses. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. The vast majority of non-invasive cancers are non-melanoma skin cancers caused by non-ionizing ultraviolet radiation. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world.