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Papel de los radicales libres y obesidad sobre el sistema nervioso central

Role of free radicals and obesity on central nervous system

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Resumen
La obesidad puede ser considerada como el síndrome del nuevo mundo, y los fármacos usados clínicamente para bajar de peso como sibutramina y orlistat actúan en niños y adultos. Los radicales libres (RL) provenientes del metabolismo normal de estas sustancias pueden ser alterados por factores exógenos. El sistema nervioso central (SNC) interviene en el control de la ingesta de alimento directamente con la participación del sistema serotoninérgico, el cual está relacionado con los medicamentos que se utilizan para bajar de peso, pero se desconoce su respuesta ante el estrés oxidante que se lleva a cabo en el SNC, por ello la importancia de presentar los hallazgos recientes de la posible relación entre obesidad, radicales libres, fármacos para bajar de peso, insulina y los más comunes desordenes neurológicos.

Abstract
Obesity could be described as the New World Syndrome and some drugs that are clinically used in weight control, like sibutramine and orlistat, act on adult and children. Most Free Radicals (FR) are generated from normal metabolic reactions, and exogenous factors can decrease or increase them, for this reason it is necessary the study of serotoninergic system and neurochemical mechanisms on the central nervous system (CNS). Considering the importance of these issues in human beings, this paper reviews the updated knowledge of possible relation between obesity, free radicals, novel antiobesity molecules, insulin and common neurological disorders.

Palabras clave: obesidad, insulina, desórdenes neurológicos, sibutramina, orlistat, SNC.

Key words: obesity, insulin, neurological disorders, sibutramine, orlistat, CNS.

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Obesity could be described as the New World Syndrome. Its prevalence is continuously increasing among people from a number of countries, irrespective of age or gender. Obesity is characterised by the excess of body fat that the most of the times, but not always, is accompanied by an increase in body weight, and it occurs when the body mass index (BMI) ≥ 30 units in the adult people. According to the latest Health National Questionnaire, overweight is represented with a 39.4% frequency in Mexico, whereas obesity had a 26.1% frequency. Obesity is better represented among women worldwide, with a frequency of 30.9%, compared with only 21.2% in men; whereas overweight is better represented in men and it occurs when the BMI > 27. BMI is higher among people with low educational level, and is associated with a risk of Parkinson disease, independent of other risk factors.

Not so long ago, an overweighing person was considered as having a healthy status, however, today it is well known that obesity carries multiple consequences in people’s health, shortens life expectancy, and induces, complicates or enhances another pathologic processes and it is now considered as a potential risk factor leading to neurodegenerative disorders. This disorders are induced to a great extent by the presence of free radicals (FR) within the CNS.

The organisms count on a protective antioxidant (AO) system that limits damage caused by free radical (FR). This protective system includes enzymes and pharmacological therapies that avoid FR generation, trap those that already exist and remove or repair damaged biomolecules. The AO system and the generation of FR coexist in a balanced way, when this equilibrium is altered the result will be oxidative stress, which can cause cell injury, trigger physiologic disorders and promote pathologic processes such as human neurodegenerative disorders, characterized by the accumulation of 8-oxo-7,8-dihydroguanine (8-oxodG) in the DNA of affected neurons, which can occur through direct oxidation of DNA guanine or via incorporation of the oxidized nucleotide during replication. A FR represents any chemical species that exists independently and has one or more unma-chetched electrons rotating in its external atomic orbits. When a FR reacts with a non-radical molecule, it can lose or gain electrons, or simply join the molecule. In any case the non-radical molecule turns into a FR and a chain reaction is triggered: one FR generates another FR. The reaction will stop only when two FR meet. The major site of production of superoxide radicals is considered to be the respiratory chain in the mitochondria, but the exact mechanism and the precise location of the physiologically relevant reactive oxygen species (ROS) generation within the respiratory chain have not been disclosed as yet. It mechanisms could be relevant, because evidence indicate that oxidative stress is a crucial factor in the pathogenesis of neurodegenerative diseases. It has been suggested that when ROS or reactive nitrogen species (RNS) production becomes exces-

Drug therapy is considered for individuals with a body mass index greater than 30 kg/m² or ranging from 25 to 30 kg/m² if they have comorbid conditions. Antiobesity agents can be helpful to some patients in achieving and maintaining meaningful weight loss, but yet our pharmaceutical tools are of limited effectiveness considering the magnitude of the problem.

Childhood obesity is emerging as a major public health threat, with adverse implications on the health of individuals and long-term costs to society. When lifestyle intervention has failed to achieve weight reduction, orlistat and sibutramine are FDA-approved for treatment of pediatric obesity. This agents promoting weight loss have beneficial effects on glycaemic parameters and need to be highlighted in order to increase their judicious use in clinical practice, although this may be limited by their well-known adverse side effects.

The use of novel drugs such as Sibutramine (N-[1-[(4-chlo-rophenyl)cyclobutyl]-3-methylbutyl]-N,N-dimethylamine HCl monohydrate) is now currently used as an alternative of long-term treatment of morbidly obese patients, which has recently been approved for prescription use in the U.S.A., Mexico and Brazil; Pharmacologically, sibutramine is known to induce hunger quenching, by inhibiting serotonine-norepinephrine turnover, although its primary amine metabolite, M2 may increase lipolysis in human adipose tissue via a pathway involving beta-adrenoceptors. Indeed, the neurotransmitters have an important role in hunger and body weight control, by decreasing calories intake, e.g., acting on the subtype 6 5-HT receptor.

Orlistat is the other novel drug for the obesity treatment. This drug has peripheral mechanism of action by selective inhibition of gastrointestinal fat thereby reducing the absorption of this in diets, and improves postprandial lipemia by reducing the absorption of the dietary fat. However, whether this drug has any interaction of the type lipophilic on central nervous system (CNS) is still unknown until now even when it is believed to control food consumption among other functions. P-Sunyer, suggest that Antiobesity drugs, such as orlistat and sibutramine, are effective weight-lowering agents in patients with type 2 diabetes mellitus, but safety and tolerability
concerns may limit their use and evidence on the clinical utility of these drugs is more equivocal, and more data are needed to evaluate the safety and tolerability of these agents.

Neurodegeneration is associated with selective neuron loss. Among the regions of the brain, hippocampus and the substantia nigra are the most susceptible to cell damage; thus, in Alzheimer’s disease. Likewise, environmental factors operating during pregnancy and postnatally may affect susceptibility genes and stress factors (e.g., cortisol), consequently affecting brain development both structurally and functionally, causing disorders becoming manifest late in life. With aging, a desynchronization of biological systems may result, increasing further brain entropy/declining criticality. In sAD, this desynchronization may involve stress components, cortisol and noradrenaline, reactive oxygen species, and membrane damage as major candidates causing an insulin resistant brain state with decreased glucose/energy metabolism.

The obesity and Alzheimer’s disease are associated with resistance of central nervous structures to the effects of insulin, which may derive from genetic polymorphisms as well as from long-term exposure to excess amounts of circulating insulin due to peripheral insulin resistance. This disorder is likely affected via a liver-brain axis whereby toxic lipids, including ceramides, cross the blood brain barrier and cause brain insulin resistance, oxidative stress, neuro-inflammation, and cell death.

Insulin is clearly neurothrophic at moderate concentrations; too much insulin in the brain may be associated with reduced amyloid-beta (Abeta) clearance due to competition for its main clearance mechanism - the Insulin-Degrading Enzyme (IDE). Since IDE is much more selective for insulin than for Abeta, brain hyperinsulinism may deprive Abeta of its main clearance mechanism, this authors suggest that clinical phenotypes associated with insulin resistance possibly represent true clinical models for brain and Morris and cols. support the hypothesis that nigrostriatal DA depletion impairs insulin signaling in the basal ganglia of PD patients.

Alzheimer’s disease (AD) is the most common form of senile dementia. AD affects 4.5 million Americans, and at least $100 billion is spent a year on direct care alone. The problem is worsening as life expectancy continues to increase. By 2050, the projected number of AD patients could range from 11.3 million to 16 million in the United States if no cure or preventive measure for AD is found. AD is manifested by a gradual onset with a progressive and irreversible cognitive decline. Memory impairment appears in the earliest stage of the disease, although patients’ motor and sensory functions are usually not affected until later stage. The neuropathology of AD is characterized by the accumulation of insoluble Ap amyloid peptides, (39–43 amino acid residues, P:d4 kDa), are the main constituent of both senile plaques and cerebrovascular amyloid deposits. These Ap peptides are generated from a much larger metalloprotein, amyloid precursor protein (APP), member of ubiquitously expressed, type-1 integral membrane glycoprotein family.

API-40 (40 amino acid residues) is the major soluble Ap species, which is found in the CSF at low nanomolar concentrations. It is generally agreed that Ap peptide neurotoxicity is dependent upon its conformational state. Synapse deterioration underlying severe memory loss in early Alzheimer’s disease could be completely prevented by insulin.

Parkinson’s disease (PD). The second most common neurodegenerative disease after Alzheimer’s, is characterized by a prevalent degeneration of dopaminergic neurons localized in the substantia nigra, if about 50-60% have been lost, one or more of the classical signs appear: resting tremor, bradykinesia, rigidity, and postural dysfunctions such as disturbances in gait or balance. Other signs and symptoms appear somewhat less frequently, including dysarthria, depression and anxiety and a reduction in the frequency of blinking and swallowing (evaluated by the Unified Parkinson Disease Rating Scale (UPDRS) part III). Although subthalamic nucleus deep brain stimulation significantly improved parkinsonian symptoms and motor complications, many patients became overweight or obese, and is important to understand the underlying mechanisms and to provide a diet management with a physical training schedule appropriate for patients with Parkinson’s disease. A novel technique Manganese-enhanced magnetic resonance imaging recently adapted to investigate the effects of gut peptides on CNS appetite circuits. Using manganese ion accumulation as a marker of neuronal activity, changes in signal intensity in key appetite centers within the hypothalamus following peripheral injection of gut hormones could help in the interactions with the CNS, because it has the potential for application in fields beyond appetite regulation.

A deficiency (80%) in the noradrenergic system of the brain, originating largely from cells in the locus coeruleus (LC) plays a decisive role in the progression of PD and the age constitutes a major risk factor and affects both sexes equally. Neuronal degeneration can depend upon a host of genetic and environmental risk factors that may include exogenous and endogenous toxins. Furthermore, chemically induced changes in gene regulation are associated with serious and complex human diseases, including obesity and neurodegenerative disorders such as Parkinson and Alzheimer diseases. With a novel method Japanese AD patients were associated with the haplogroups G2a, B4c1, and N9b1 and Japanese PD patients with M7b2, B4e, and B5b. This analysis method can predict the probabilities of becoming an AD patient or PD patient. Until now there is no known cure for PD, and usually L-DOPA offers symptomatic relief.
Historically, the epidemiology of disease risk factors has centered on adult life, with little scrutiny of early-life events. Suspect events in early life include infections, stress, poor nutrition, and environmental factors such as chemical and pesticide exposure. Adiposity appears to contribute to both PD and AD; and because early-life events contribute to the development of obesity, linkages may exist between early determinants of obesity and the subsequent development of these neurologic diseases. The studies for PD and AD suggest that a number of insults occurring early in life may lead or contribute to these diseases.

Conclusion

Definitive knowledge of the key risk factors involved in obesity treatments will be needed to implement intervention and preventative strategies early in life to dampen or prevent any adverse late-life outcomes.

References


