CHAPTER ONE

INTRODUCTION

High-fat diets are dietary plans that consist of a high percentage of calories from fats, typically more than 30-35% of total daily caloric intake. These diets often include foods rich in fats such as meat, dairy products, nuts, oils, and fatty fish. High-fat diets can vary in their specific compositions and health impacts. They are sometimes used in weight loss and management strategies, like the ketogenic diet, which is high in fat and low in carbohydrates. (Johnston *et al*.,2014). A recent study stated that Western-style diets, which are high in refined sugars and saturated fats, have a greater likelihood of inducing memory impairment in healthy subjects (Jena, 2018).

Holloway *et al.*, 2011 found that HFD administration (nearly 75% of energy) for five days is sufficient to induce depression and impair retrieval speed and attention. Carey and Galli (2017) also reported that HFD influence the brain negatively. However, the part of the brain this negative influence is seen is limited. This very possible gap in knowledge is one of the reasons for this review.

Apart from the HFD, Bisphenol-A (BPA) is also another chemical that has been reported to influence the brain negatively (Costa and Cairrao, 2024).

BPA is a widespread industrial chemical with endocrine-disrupting properties, found in various consumer products like plastics and resins (Rubin, 2011; Vandenberg *et al.*, 2007).

It provides an effective barrier preventing chemical reactions between the food and the metal wall of the bottle, thereby ensure food safety. Also it is a building block in industrial production of polycarbonate plastics as baby bottles, tableware, food containers, water bottles and dental sealants (Calafat *et al*., 2005; Rubin 2011). It can also be found as a residue in paper and cardboard food packaging materials (Lopez-Espinosa *et al*., 2007).

BPA in food and beverages accounts for the majority of daily human exposure contributes to 10-40% of the daily intake (von Goetz *et al*., 2010). Bisphenol-A can migrate from the containers into the liquid. The degree of its migration depends more on the temperature of the liquid than the date of manufacture as more migration occurs with higher temperatures (Le *et al*., 2008). Also BPA has wide spread exposure, it causes air pollution and water stream contamination (Covington, 2004).

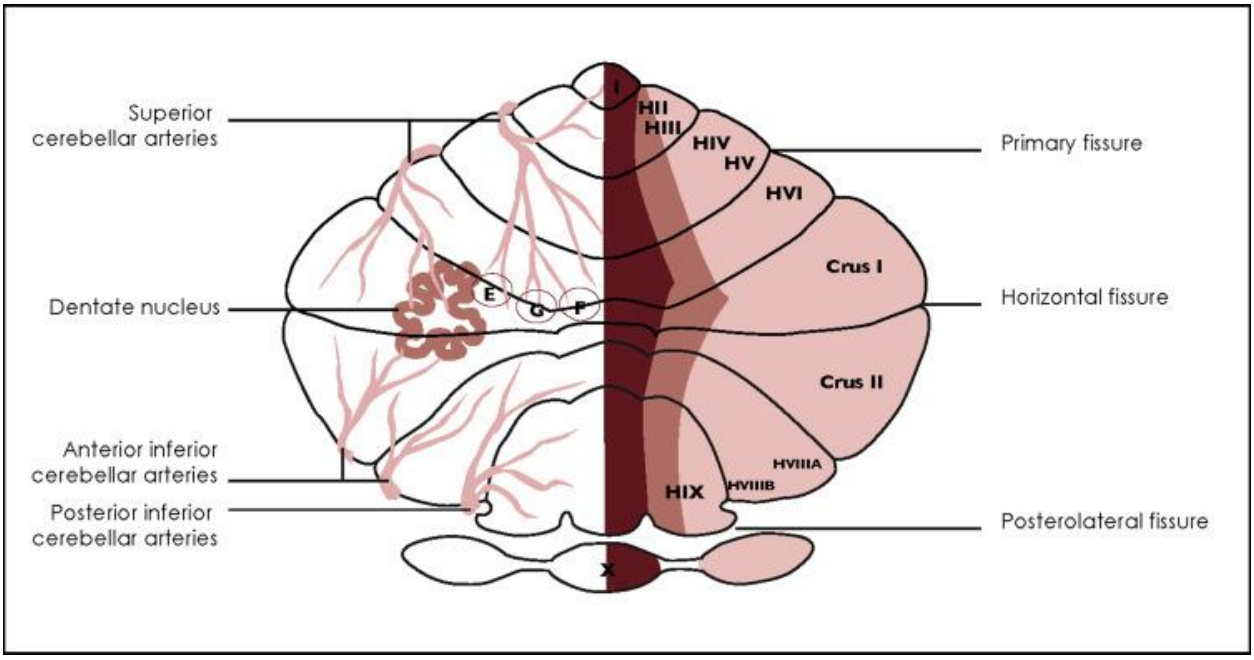
This review seeks to examine the combinatory effects of HFD and BPA on the cerebellum.

CHAPTER TWO

LITERATURE REVIEW

2.1. Cerebellum

Cerebellum is one of the structure in the brain that begins first to differentiate but last to mature since its development is spread over a longer period and shows age related changes (Standring *et al.,* 2008). Cerebellar cortex is divided into outer molecular layer, middle Purkinje cell layer and inner granular layer. External granular layer appears first on the surface of the cerebellum as a dense layer of cells at third embryonic month. External granular was precisely described by Obersteinerand, he observed that the cells in the outer layer form the basal membrane and cells of the inner layer enter into the molecular layer and migrate through this into the inner granular layer. External granular layer consists of indifferent cells that may convert into either nerve cells or glial cells, (Schaper 1894). External granular layer is the precursor of purkinje cell and internal granular cell layer, (Popoff 1895).



Lobes and lobules are separated from each other by fissures. Each lobule is composed of folds of cerebellar cortex called folia. The anterior lobe can be divided into lobules I–V, the posterior lobe into lobules VI–IX, and lobule X is the flocculonodular lobe. Furthermore, lobules VII can be subdivided into Crus I, Crus II, and VIIB and lobule VIII into VIIIA and VIIIB (Donkelaar, 2018). Each of the cerebellar lobules is thought to have its own functional role and is connected to the neocortex in a specific pattern. Lobulus HI is usually absent. This scheme emphasizes the transverse continuity of lobules across the vermis (dark red), paravermis (light red), and the hemispheres (pink).
E, emboliform nucleus; F, fastigial nucleus; G, globose nucleus.
Figure by courtesy of I. Koning.

2.1.1. Histology

After slicing the cerebellum, it bears a similar resemblance to a cauliflower. This is due to the stemmed appearance of the white matter coated by the outer grey matter of the cortex. When viewing a histological section of cerebellar tissue under the microscope, the lobulations and folia of the cerebellum are immediately evident. (William K. O, *et al.*, 2013).

These folia are the leaflike gyri of the cerebellar cortex. The extensive vascular supply will also be evident, as a high blood flow is required to meet the demands of the cerebellum's neural activity. The pia mater, the innermost layer of the meninges, which covers and protects the cerebellum is also likely to appear surrounding the perimeter of this structure in a stained section. (Mescher Anthony L)

As previously mentioned, the grey matter of the cerebellum is also referred to as the cortex and may be split into three layers; the outer molecular layer, the middle layer of Purkinje cells and the inner granular layer. There are many neurons, glial cells and fibers located in the cortex which all contribute to the motor functions of the cerebellum. (Ross M. H.,).

2.1.2. Embryology

The neural plate, derived from the thickening of ectodermal tissue, is the precursor for all components of the central nervous system. Through a process called neurulation the neural plate folds during the fourth week of gestation to become the neural tube. The rostral portion of the neural tube divides into the prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain). The rhombencephalon further divides into the metencephalon and myelencephalon. The cerebellum is derived from the dorsal part of the metencephalon, specifically the alar plate, and the neural folds. (Balaei *et al.,* 2017).

Neurons found in the cerebellum are derived from two germinal zones; the ventricular zone and the rhombic lip. The ventricular zone is the neuroepithelium of the alar plate which later develops into the roof of the fourth ventricle. Purkinje cells, Golgi cells, stellate cells, basket cells and candelabrum cells are just some of the neurons derived from this particular zone.

Neurons derived from the rhombic lip include large neurons of the cerebellar nuclei, unipolar brush cells and granule cells.

These 2 groups of neurons are distinguishable by the neurotransmitter they release. Neurons from the ventricular zone are inhibitory GABAergic neurons, while those from the rhombic lip are excitatory glutamatergic.

2.2. The cerebellum and its Combinatory Effects

The cerebellum, a critical part of the brain involved in motor control, cognitive functions, and emotional regulation, is vulnerable to various environmental factors, including exposure to endocrine-disrupting chemicals (EDCs) and dietary habits. Bisphenol-A (BPA), a synthetic compound found in many consumer products, is an EDC with widespread human exposure. Similarly, high-fat diets (HFDs) are prevalent in many modern societies and are linked to various health problems, including obesity and metabolic disorders. Emerging evidence suggests that the combination of BPA exposure and an HFD may have synergistic and detrimental

effects on the cerebellum, leading to significant neurodevelopmental and neurofunctional impairments.

2.2.1. Mechanisms of Neurotoxicity

Bisphenol-A (BPA) Neurotoxicity: BPA acts as an estrogen mimic, binding to estrogen receptors and disrupting normal hormonal signaling. In the brain, BPA has been shown to induce oxidative stress, neuroinflammation, and alter neurotransmitter levels. Specifically, in the cerebellum, BPA exposure has been linked to impaired function of Purkinje cells, a type of neuron crucial for motor coordination and cognitive processes. BPA's ability to disrupt synaptic plasticity and neurotransmission may lead to deficits in motor and cognitive functions (Ben-Jonathan *et al.,* 2009).

High-Fat Diet (HFD) Effects: A high-fat diet can lead to obesity, which is associated with systemic inflammation, insulin resistance, and metabolic dysregulation. In the brain, HFD has been shown to increase neuroinflammation, oxidative stress, and disrupt neuronal signaling. The cerebellum, with its high density of polyunsaturated fatty acids, is particularly vulnerable to oxidative damage. HFD-induced neuroinflammation in the cerebellum can impair the function of glial cells and neurons, leading to deficits in motor control and cognitive function (Ross & Bruggeman, 2018).

2.2.2. Synergistic Effects on the Cerebellum

When BPA exposure is combined with a high-fat diet, the neurotoxic effects on the cerebellum may be amplified. Both BPA and HFD independently contribute to oxidative stress and neuroinflammation, but their combination can lead to more severe neurodegenerative outcomes.

Oxidative Stress: BPA and HFD both increase the production of reactive oxygen species (ROS) in the brain. The cerebellum's high metabolic activity and lipid content make it particularly susceptible to oxidative stress. Combined exposure to BPA and HFD may overwhelm the brain's antioxidant defenses, leading to increased neuronal damage, apoptosis, and loss of cerebellar neurons, particularly Purkinje cells. This oxidative damage can result in impaired motor coordination and cognitive deficits (Yang & Li, 2021).

Neuroinflammation: Chronic exposure to BPA and HFD can lead to sustained activation of microglia, the brain's resident immune cells, resulting in the release of pro-inflammatory cytokines. This chronic neuroinflammation can exacerbate neuronal damage and disrupt normal cerebellar function. The synergistic effect of BPA and HFD may lead to more pronounced neuroinflammation, further impairing motor and cognitive functions associated with cerebellar dysfunction (Rocha *et al.*, 2019).

Synaptic Plasticity: Synaptic plasticity, which is critical for learning, memory, and motor coordination, can be disrupted by both BPA and HFD. The combination of these factors may lead to more significant impairments in synaptic function within the cerebellum, resulting in long-term deficits in motor skills, learning, and memory. This disruption in synaptic plasticity can compound the effects of cerebellar damage, leading to more severe neurofunctional impairments (Marques & Frost, 2017).

2.3. CEREBELLAR COMPARTMENTALIZATION AND MICROZONES

Histologic examination of the cerebellar cortex reveals a homogeneous sheet of tissue with a stereotypical internal structure. (Apps *et al*., 2009).

However, this structure has been compartmentalized using anatomic, molecular, and physiologic approaches to longitudinal zones. (Apps *et al.*, 2009).

A longitudinal zone is a narrow, rostrocaudally extended sagittal region of the cerebellar cortex in which Purkinje cells receive climbing fiber inputs from specific subregions of inferior olive and project to specific cell groups of the deep cerebellar nuclei. Each of these nuclear subregions in turn projects to a specific set of targets in the central nervous system.

Vermis, paravermis, and cerebellar hemispheres are each divided into 3 to 5 longitudinal zones from midline to lateral. Each longitudinal zone could be further

subdivided to even narrower compartments known as microzones. (Apps *et al.*, 2009).

The Purkinje cells of each microzone have a similar somatotopic receptive field (ie, activated by an essentially identical peripheral stimulus) and receive climbing fiber inputs from a cluster of inferior olivary neurons that are coupled together by gap junctions. These Purkinje cells project to particular clusters of neurons in the deep cerebellar/vestibular nuclei, and part of the nuclei output projects back to the same cluster of olivary neurons. Molecular layer interneurons and Golgi cells' inputs and outputs are also limited to the microzones they belong to. Given that the parallel fibers tend to span multiple sagittal zones, microzones are not unique in their mossy fiber inputs. The combination of microzones along with their associated clusters within inferior olivary and deep cerebellar nuclei could be regarded as functional units (modules) of the cerebellum. Thus, cerebellum is regarded as a computational machine consisting of a large number of almost independent modules, which are similar in terms of internal structure, and as such, perform the same computation on any kind of input (motor or nonmotor) that they receive. In addition, several spatially distinct microzones receiving inputs from the same olivary neurons form multizonal microcomplexes that may have a crucial role in parallel processing and integration of information from a multitude of mossy. (Apps *et al.*, 2009).

2.4. CEREBELLAR PLASTICITY AND LEARNING

Recordings from cerebellar neuronal activities in vitro and in vivo, under natural conditions and after pharmacologic and genetic manipulations, have greatly contributed to the current understanding of the physiologic basis underlying cerebellar motor performance, motor learning, and consolidation. (De Zeeuw *et al.*, 2011).

These studies suggest that, in addition to the rate of neuronal firing, the spatiotemporal firing pattern of Purkinje cells also play an important role in cerebellar coding. (De Zeeuw *et al.,* 2011).

The electrical activity of Purkinje cells is characterized by a combination of simple and complex spikes. Simple spikes are single action potentials and their firing pattern is determined by the intrinsic activity of Purkinje cells, together with their inputs from parallel fibers and molecular layer interneurons. Complex spikes are sequences of short-interval action potentials with diminishing amplitudes that are generated in response to olivary neuron inputs through climbing fibers. Olivary neurons innervating a given microzone show coherent and synchronous firing pattern and subthreshold membrane potential oscillations. Inputs from external stimuli can reset the phase of these subthreshold oscillations, which in turn may

influence the temporal pattern of Purkinje complex spikes and lead to switching to a different motor program mode. (De Zeeuw *et al.,* 2011).

As with complex spikes, simple spike firing patterns are also best preserved within microzones Climbing fibers are believed to convey the error signals to the cerebellum. (Apps *et al.,* 2005).

These signals are crucial for motor learning because they could help cerebellum adapt the motor commands based on errors from prior movements.

At the level of the cerebellar cortex, the timing of climbing and parallel fiber activation with respect to each other is critical for cerebellar plasticity and learning. Coincidence of inputs from these 2 fibers leads to a distributed and synergistic plasticity (Gao *et al.,* 2012).

These signals are crucial for motor learning because they could help cerebellum adapt the motor commands based on errors from prior movements. At the level of the cerebellar cortex, the timing of climbing and parallel fiber activation with respect to each other is critical for cerebellar plasticity and learning.

Coincidence of inputs from these 2 fibers leads to a distributed and synergistic plasticity (Gao *et al*., 2012) within the cerebellar functional modules. Plasticity is distributed in the sense that it occurs along almost all types of synapses (both at the level of cerebellar cortex and deep nuclei) and intrinsic neuronal excitability within

the cerebellar circuitry, and it is synergistic in the sense that long- or short-term depression at excitatory synapses occurs in coordination with long- or short-term potentiation at inhibitory interneuronal connections, and vice versa.

Abnormal expression of ion channels or defective channels in the cerebellar neurons lead to inappropriate excitability of the cells, alter their firing rates or spike patterns, and impede proper neuronal plasticity.

Investigators have posited that such cerebellar channelopathies contribute to cerebellar deficits in ataxic disorders. (Shields *et al*., 2012).

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2.5. HIGH FAT DIET (HFD)

2.5.1. COMPOSTION OF HIGH FAT DIET (HFD)

INGREDIENTS	DIETS(g/kg)
Powdered NPD	365
Butter	310
Casein	253
Cholesterol	10
Vitamin and mineral mix	60
Yeast powder	1
Sodium chloride	1

(Mahmoud *et al.*, 2016).

INGREDIENTS	Percentage of HFD
Powdered Normal Pellet Diet (NPD)	73%
Cholesterol	1%
Tallow	10%
Egg yolk powder	10%
Milk Powder	6%

(Alkholifi *et a.l,* 2021).

Ingredients	Diet(g/100g) High Fat Diet	Normal Chow Diet
Chow	54.0	100.0
Oil	4.8	-
Lard	12.7	-
Condensed milk	28.5	-
Carbohydrate	41.7	48.7
Fat	22.5	5.0
Protein	15.0	23.9

(Kao *et al.*, 2018).

2.5.2. Disease conditions related to HFD

In the last decade, more scientific interest in nutrition-related effects on brain function has emerged. Rates of obesity, diabetes, and dementia continue to climb and both retrospective and prospective studies suggest that obesity and increased consumption of high-fat diets increases risk for development of dementia. (Kalmijn *et al.*, 1997 and Luchsinger *et al.*, 2002).

2.5.3. Effect of diet on cognition

Diet composition	**Cognitive results**	**Postulated biological mechanism**	
Lard-based diet (40% calories from fat)	Worse performance on working memory and retention	Not discussed	(Greenwood *et al.*, 1990).
Lard & corn oil (39% energy)	Worse performance on Morris water maze	Oxidative stress, reduced BDNF levels	(Wu *et al.*, 2004).
High fat diet (45% calories from fat)	Worse performance on operant-based delayed matching to position task	Insulin resistance	(McNeilly *et al.*, 2011).
High fat, high glucose diet supplemented with high fructose corn syrup	Worse performance on a spatial learning task	Insulin resistance, Reduced BDNF levels	(Stranahan *et al.*, 2008).
High saturated fat and cholesterol	Worse performance on the Water Radial Arm Maze	Inflammation, reduced dendritic integrity in the hippocampus	(Freeman *et al.*,2011).
'Western diet' (41% calories from fat) or	Impaired retention on behavioral test	Oxidative stress	(Morrison *et al.*, 2010).

Lard (60% calories from fat)	for 60% fat but not 'Western diet'		
High fat diet (45% calories from fat) + Metformin	Improved performance on operantbased task	Insulin sensitivity	(McNeilly *et al.*, 2012).
High-fat high-carbohydrate + Vitamin E	Improved performance on Water Radial Arm Maze	Oxidative stress	(Alzoubi *et al.*, 2013).
High fat diet (45% calories from fat)	Impaired performance on Fear Conditioning Task	Oxidative stress	(Freeman *et al.*, 2013).
High fat diet + Sugar	Impaired performance on serial feature negative task	Vascular/adiposity	(Davidson *et al.*, 2012).

CHAPTER THREE

3.1 Effects of High-Fat Diet on Cerebellum

Two families of essential fatty acids; omega-3 and omega-6 are required for normal body growth and maturation of many organs, most importantly the brain and eye. Fish and fish oil are rich sources of omega3 fatty acids, specifically eicosapentaenoic acid and docosahexaenoic acid (KRIS-ETHERTON *et al.*, 2003).

Alpha-linolenic acid is an omega-3 fatty acid present in seeds, green leafy vegetables, nuts as walnuts and beans as soybeans (KRIS-ETHERTON *et al.*, 2000).

Omega-3 fatty acids are found in high concentrations in neuronal membranes and have antioxidant properties (SARSILMAZ *et al.*, 2003).

Omega 3 is available in the form of soft gelatin capsules from SEDICO; Pharmaceutical Company, Cairo, Egypt. Each capsule contains 1000mg of omega 3. According to (COVINGTON 2004), 3000mg/day omega 3 was used in this work.

It is the average human therapeutic dose

In human epidemiological studies, it has been shown that intake of a high-fat diet that includes mostly omega-6 and SFAs is associated with worse performance on a cognitive task (Kalmijn *et al.*, 1997).

Furthermore, studies have shown that a diet containing mostly SFAs and TFAs is associated with increased risk for Alzheimer's disease. On the other hand, a lower fat diet consisting of omega-3 fatty acids had a protective effect against cognitive decline in healthy older subjects.

It has also been determined that high consumption of total fats, SFAs, and cholesterol is associated with increased cholesterolemia, risk of cardiovascular disease, and impaired intellectual function, suggesting that the circulating levels of cholesterol are closely associated with cognitive performance in humans (Requejo *et al.*, 2003).

3.2 Combinatory Effects of HFD and BPA on neuronal structures

Neuro-inflammation and Oxidative Stress: Both a high-fat diet and BPA exposure have been associated with increased neuro-inflammation and oxidative stress, which can lead to damage to neuronal structures. (Hsu *et al*., 2019).

Disruption of Synaptic Plasticity: Studies have shown that high-fat diet and BPA exposure can interfere with synaptic plasticity, which is crucial for learning and memory. (Li *et al*., 2017).

Impaired Neurodevelopment: Prenatal or early-life exposure to a high-fat diet and BPA can have detrimental effects on neurodevelopment, leading to structural abnormalities in neuronal networks. (Morales-Prieto *et al*., 2019).

Altered Neurotransmitter Systems: Both a high-fat diet and BPA exposure have been implicated in changes in neurotransmitter systems, including disruptions in dopamine and glutamate signaling. (Specterman *et al.,* 2019).

3.3 Inflammatory Response

"Inflammation is a biological response of the immune system that can be triggered by a variety of factors, including pathogens, damaged cells, and toxic compounds" (Acaroz *et al.,* 2019). Consequently, an inflammatory response is initiated and is defined as "the coordinate activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood" (Chen *et al.,* 2018). It has been shown that exposure to BPA can alter the production of inflammatory cytokines and subsequently cause an immune dysfunction (Acaroz *et al.,* 2019).

It has been reported that the chronic oral exposure of mice to BPA leads to an increased brain mRNA expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), and decreased anti-inflammatory IL-10 (Acaroz *et al.,* 2019). Therefore, this demonstrates the BPA capacity to induce a pro-inflammatory response within the CNS. This local inflammatory response must be regulated by the cells that reside in the CNS.eg. microglia.

3.4. Bisphenol A and its neurological effects

Neurovascular diseases are a type of neurological disease and are of extreme concern to humans, as they can be fatal or cause permanent disability. Neurovascular diseases affect the cerebral vascular system and the spinal cord. These diseases can be caused by deformations in the endothelium layer, smooth muscle layer of blood vessels, and other molecular bases of pathogenesis (Sam *et al*., 2015).

Because sex steroids are widely thought to play critical roles in higher brain activities, such as cognition and mood, through modulating structural and functional synaptic plasticity (Liu *et al*., 2008, Hajszan and MacLusky 2006, Li *et al*., 2004), our findings suggest that exposure to low-dose BPA may have widespread effects on brain structure and function.

An important limitation of previous studies of BPA is that the studies were based on rodent animal models. One argument defending the safety of BPA use is that the clinical predictive power and experimental utility of rodent studies is limited, due to dissimilarities between rodent and human endocrine systems and brains. Thus, it is conceivable that the adverse effects of BPA observed in rodents might not occur in primates, including humans, within the dose range expected from normal environmental exposure.

3.5. BPA's effect on neurodevelopmental disorders

"Neurodevelopmental disorders (NDD) are highly prevalent and severely debilitating brain illnesses caused by aberrant brain growth and development" (Homberg *et al*., 2016). They cause cognitive, social, motor, language, and affective disabilities.

3.6. ROLE OF BISPHENOL A IN DIABETICS AND OBESITY

Bisphenol A is a compound commonly found in products meant for daily use. It was one of the first compounds to be identified as an endocrine disruptor that was capable of disrupting the endocrine system and producing very similar effects to those of metabolic syndrome. It has recently gained popularity in the scientific arena as a risk factor for obesity and diabetes due to its ability to imitate natural oestrogens and bind to their receptors.

Bisphenol A is an additional risk factor to consider in the development of diabetes and obesity, since it is capable of stimulating the hypertrophy of adipocytes and altering the endocrine system by mimicking the effects of the oestrogen molecule.

3.7. clinical implications

The number of overweight or obese youths has tripled in the last three decades, increasing faster than obesity rates in adults in most countries (BD 2015 Obesity

Collaborators. Afshin A., Forouzanfar M.H., Reitsma M.B., Sur P., Estep K., Lee A., Marczak L., Mokdad A.H., Moradi-Lakeh M., *et al.*, 2017)

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body does not use the insulin effectively. The effect of uncontrolled diabetes is hyperglycaemia (increased blood sugar), which over time seriously damages many organs and systems, especially nerves and blood vessels [World Health Organization Diabetes].

Type 2 diabetes mellitus (DM2) is the most frequent form of presentation, accounting for 90% of the total cases. Type 1 diabetes mellitus (DM1) cases represent 5 to 10% of total cases and the remaining percentage corresponds to other forms of presentation. The prevalence is increasing rapidly due to the improvement in life expectancy and changes in lifestyle habits [World Health Organization Diabetes.].

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disorder characterized by peripheral insulin resistance, β-cell dysfunction and an inadequate compensatory insulin secretory response (Chatterjee *et al*., 2017).

3.8. POSSIBLE LINK TO NEUROLOGICAL DISORDERS

1. **Developmental and Behavioral Effects:** Animal studies have indicated that exposure to BPA during critical developmental periods may affect brain

development and behavior. This could potentially lead to issues like hyperactivity, altered learning, and memory deficits.

2. **Endocrine Disruption:** BPA is known as an endocrine disruptor, which means it can interfere with hormonal signaling in the body. Hormones play a crucial role in brain development and function, so disruptions caused by BPA might have neurological consequences.
3. **Inflammation and Oxidative Stress:** BPA exposure has been associated with increased inflammation and oxidative stress in the body. These factors are implicated in various neurological disorders, including Alzheimer's disease, Parkinson's disease, and others.
4. **Neurological Development:** There are concerns that BPA exposure, particularly during fetal development, infancy, and childhood, might affect the wiring and functioning of the nervous system, potentially increasing susceptibility to neurological disorders later in life.

CHAPTER FOUR

4.1. CONCLUSION

Understanding the combinatory effects provides insights into potential synergistic risks that are more severe than individual exposures. This highlights the need for comprehensive risk assessments and regulatory policies addressing combined environmental and dietary factors.

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