Physiological Mechanisms of Cognition and Diabetes Mellitus

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Abstract

Diabetes mellitus (DM), a metabolic disorder characterized by hyperglycemia, significantly impacts cognitive function, manifesting as mild cognitive impairment (MCI) or even dementia. This abstract explores the intricate physiological mechanisms underlying this cognitive decline, emphasizing the multifaceted interplay between glucose dysregulation and brain health. Hyperglycemia directly damages neuronal structures and functions through several pathways. Advanced glycation end products (AGEs) accumulate, contributing to oxidative stress, inflammation, and impaired neurotransmission. This oxidative burden reduces cerebral blood flow, leading to neuronal hypoxia and dysfunction in crucial cognitive regions like the hippocampus and prefrontal cortex. Furthermore, chronic hyperglycemia disrupts the blood-brain barrier (BBB) integrity, promoting neuroinflammation and facilitating the entry of harmful molecules into the brain parenchyma. Beyond direct effects, DM affects several neurotransmitter systems critical for cognition. Insulin resistance, often accompanying DM, impairs insulin signaling in the brain, impacting neuronal plasticity, synaptic function, and memory consolidation. Alterations in acetylcholine, glutamate, and other neurotransmitters contribute to cognitive deficits observed in DM. Furthermore, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, frequently seen in DM, leads to chronic stress and increased cortisol levels, which exacerbate neuronal damage and impair cognitive performance. Vascular complications, a hallmark of DM, further contribute to cognitive decline. Microvascular disease, including cerebral small vessel disease, leads to white matter hyperintensities, reduced cerebral perfusion, and consequent cognitive impairment. Macrovascular complications, such as stroke, directly damage brain tissue, resulting in significant cognitive deficits. The interplay of these micro and macrovascular pathologies underscores the complex relationship between vascular health and cognitive function in DM. Addressing these underlying physiological mechanisms through robust glucose control, lifestyle interventions, and potential novel therapeutic targets is crucial for preventing and managing cognitive decline associated with DM. Future research should focus on identifying early biomarkers and developing targeted interventions to mitigate the cognitive burden of this prevalent metabolic disorder.

Keywords: Physiological mechanisms , cognition, Diabetes Mellitus

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Introduction

Cognition can be described as "information processing." This definition includes the acquisition of sensory information, the storage, retrieval, and use of that information for making behavioral decisions [1]. The word "cognition" is of Latin derivation but originally comes from the Greek verb "gignosko" which means to recognize, perceive, and know [2]. The Oxford English Dictionary (OED) notes cognition traces its roots to the Latin noun *cognitio* ('examination,' 'learning,' or 'knowledge'), derived from the verb *cognosco*, a compound of *con* ('with') and *gnōscō* ('know') [3]. Specifically, cognition is the mental action or intellectual process of acquiring, understanding, and using knowledge or information, through thinking, experience, and the senses, by which human behavior can be adapted to new situations and/or preferences changed [4].

Cognition and Neuropsychological Domains

Cognition involves different cognitive processes which can be divided into six key basic neuropsychological domains which in turn are divided into subdomains. The key cognitive functions include learning and memory, visuospatial and motor function, attention/concentration, language, social cognition/emotions, and executive functions. Each domain contains specific functions which provide individuals with basic and more complex capabilities that determine personal intellectual skills and knowledge [5] (Figure 1).

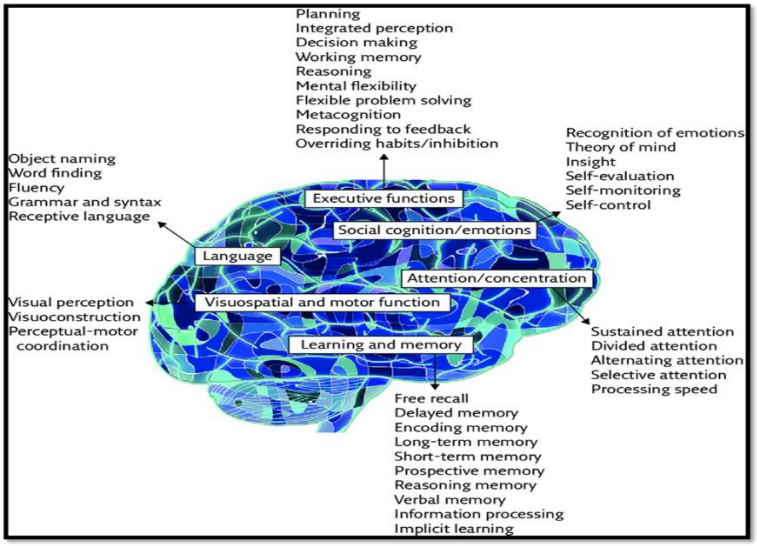

Figure (1) Major domains of cognitive function [4]

Domains of Cognition and Their Assessment

The characterization and classification of cognitive performance in clinical neuropsychology refer to domains of cognitive performance. Within each domain, there are typically subdomains, which refer to component ability processes within the larger constructs. There are several ways to conceptualize cognitive ability domains. These include classification by the general process

involved, such as memory or attention, language, or executive functioning. Other strategies are based on regional brain functions, derived on the basis of lesion studies, which characterize functions as originating from the frontal lobe, temporal lobe, parietal lobe, hippocampus, or other structures. An additional organizational structure is hierarchical and based on the complexity of the operations [6].

There is no clear-cut border between cognitive, emotional, and volitional functions as cognition comprises a volitional component and influences emotional reactions and decision-making. When the information process takes place, it engages the cognitive functions in a specific order. Information obtained by the sensory systems is selected for further processing with the aid of attention. The selected information can then be retained over shorter time periods by a working-memory system [7].

Most cognitive capacities develop from infancy through childhood and adolescence into adulthood and reflect the maturation of the central nervous system over time. By 10 years of age, when the brain has begun to reach its adult size, children have already undergone substantial development in cognitive functions. Cognition continues to develop in parallel with a refinement of neural networks via synaptic strengthening and pruning as well as myelination [8].

Cognitive Status Measures

The most widely used tests which cover multiple cognitive domains are the Mini Mental State Examination (MMSE), the Addenbrooke's Cognitive Examination (ACE), the Montreal Cognitive Assessment (MoCA), the Clock Drawing Test (CDT), and the Mini-Cog test [4]. The Japanese language version of the Mini-Mental State Examination (MMSE) is widely used for the evaluation of cognitive function and cognitive impairment screening. The MMSE score ranges from 0 to 30, with lower scores representing weaker cognitive function [9].

Testing of cognitive functions in rodent disease models constitutes a substantial sector of behavioral neuroscience. It is important to realize that no behavioral test is specific for a single cognitive domain. There are numerous noncognitive factors that may lead to impaired performance in most widely applied memory tasks. It is important to rule these out by applying a battery of tests that should include at least tests for motor functions, spontaneous activity, and anxiety besides cognitive aspects [10].

Factors Affecting Cognition

a) **Age:** Healthy aging is associated with numerous deficits in cognitive function, which have been attributed to changes within the prefrontal cortex anatomy and physiology, with a particular role of suboptimal dopamine levels that may have a genetic basis. Specifically, aging of the prefrontal cortex results in deficient aspects of cognitive control, including sustained attention, selective attention, inhibitory control, working memory, and multitasking abilities. Yet, not all cognitive functions associated with the prefrontal cortex exhibit age-related declines, such as arithmetic, comprehension, emotion perception, and emotional control. Moreover, not all older adults exhibit declines in cognition [11].

The most important changes in cognition with normal aging are declines in performance on cognitive tasks that require one to quickly process or transform information to make a decision,

including measures of speed of processing, working memory, and executive cognitive function. Cumulative knowledge and experiential skills are well maintained into advanced age. Structural and function changes in the brain correlate with these age-related cognitive changes, including alterations in neuronal structure without neuronal death, loss of synapses, and dysfunction of neuronal networks. Age-related diseases accelerate the rate of neuronal dysfunction, neuronal loss, and cognitive decline, with many persons developing cognitive impairments severe enough to impair their everyday functional abilities [12].

In aging, many but not all cognitive functions begin to decline. Examples of cognitive functions that are well-preserved into older age include memory for facts, social cognition, and more general functions that tap into well-consolidated information. Age-sensitive cognitive functions include working memory, certain forms of attentional functions, episodic long-term memory, and several executive functions. The normal variation in cognitive capacity between individuals increases with age, and while some older adults show marked cognitive decline, others maintain high levels of cognitive functioning [7].

b) **Genetics:** Some studies have connected cognitive function with certain genes. It was found that a person's level of brain-derived neurotrophic factor (BDNF), which is 30% determined by heritability, can impact the rate of brain neurodegeneration, a condition that ultimately impacts cognitive function. The genetic determinants and biological implications of variation in circulating BDNF levels, an intriguing molecule that affects many aspects of physiology ranging from memory, mood, and cardiac function to smoking habits; BDNF may also be a biological mechanism through which physical and social activities, diet, and other lifestyle factors influence disease risk [13].

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophins superfamily, plays an important role in brain development and function, regulates growth and survival of neurons, promotes long-term potentiation and modulates synaptic transmission and activity-dependent plasticity [14]. Substantial amounts of BDNF are present in peripheral blood and may serve as biomarkers for Alzheimer's disease incidence as well as targets for intervention to reduce Alzheimer's disease risk [15].

c) **Nutritional Status:** Optimal nutrition during childhood is necessary for normal brain development of children since it is an important period for the formation of the brain, laying the foundation for the development of cognitive, motor, and socio-emotional skills throughout their life. On the other hand, poor nutrition during the early period can result in long-lasting physical and mental impairment by affecting the structural and functional development of the brain. So, malnutrition may play an important role in the progression of cognitive loss [16].

d) **Memory Limitations:** Short-term memory is surprisingly brief, typically lasting just 20 to 30 seconds, whereas long-term memory can be stable and enduring, with memories lasting years and even decades. Memory can also be fragile and fallible [17].

e) **Attention Issues:** Selective attention is the process of attending to information that is relevant and important and ignoring other nonrelevant information. Selective attention tasks often provide distracting information and request the examinee to attend specifically to the relevant

information. Distractors can be presented in an opposite-sexed voice for auditory tasks and otherwise identified as irrelevant (font color, size) for visual tasks [6].

Types of Cognitive Processes

1. **Learning:** Learning is a basic cognitive activity, a process of accumulating experience and knowledge and a process of understanding external things to improve the performance of system behavior. The neurobiological basis of learning is the synaptic plasticity of the connection structure between nerve cells. The synaptic plasticity condition is that when the presynaptic fibers and the associated postsynaptic cells are excited at the same time, the synaptic connection is strengthened [18].

2. **Memory:** Memory is the process of retaining knowledge over a period for the function of affecting future actions. Memory functioning is the most complex and multifaceted of cognitive domains. Memory is an important cognitive process that allows people to encode, store, and retrieve information. It is a critical component in the learning process [6].

Classification of memory: There are four main categories of memory. All other types of memory tend to fall under these four major categories. Memory is sometimes also classified into stages and processes. People who classify memory into only two distinctive types, implicit and explicit memory, view that other types of memories like sensory, short-term, and long-term memories aren't types of memory but stages of memory [19].

1- **Sensory Memory:** Sensory memory consists of three types. The first is the iconic memory. It is a quickly declining storage of visual data. It stores an image for a small duration which has been perceived by the person briefly. The second is the echoic memory. It is described as storage of sounds for short durations that have been heard briefly. Moreover, haptic memory characterizes a database for touch stimuli [20].

2- **Short-term memory (STM):** Short-term memory (STM), also referred to as short-term storage, or primary or active memory, indicates different systems of memory involved in the retention of pieces of information (memory chunks) for a relatively short time (usually up to 30 seconds) [21].

3- **Working memory:** Working memory can fall under the classification of short-term memory and, in many cases, is even used interchangeably. Working memory is the ability to maintain and manipulate information in the conscious mind over a timescale of seconds. This ability is thought to be maintained through the persistent discharges of neurons in a network of brain areas centered on the prefrontal cortex. It is a critical cognitive function in the ability to learn, make decisions, and function in daily life [22].

4- **Long-term Memory:** Long-term memory was classified into two main categories: declarative (explicit) and procedural (implicit) memories [23].

a) **Explicit/declarative/Episodic memory:** Explicit memory can be defined as the information regarding places, things, people, and events, etc. It can be recollected by conscious effort. It is stored in the medial part of the temporal lobe of the cerebrum and hippocampus. It may be subdivided into episodic memory which is also called autobiographic memory and semantic memory [24]. Episodic memory is the ability to consciously recall personal events and

experiences. Whereas semantic memory recalls facts which can be general or autobiographical. And it's different from the semantic memories in that you can remember the exact time and place in which the event occurred, or you gained that information. In general, episodic memory occurs through extensive connections between the neocortex and the Para hippocampal regions and the hippocampus (HPC), and the HPC is considered the most critical structure in forming episodic memory. Not all areas that support the generation of episodic memory are activated at the same time, nor in all tasks [25]. This component of the memory system interacts with working memory storage processes to encode, maintain, and retrieve information into and out of longer-term storage. Memory information can be from all sensory types and can also be verbal or nonverbal [6].

Semantic memory, the long-term memory for facts, is closely related to language functions. This refers to the process of long-term storage of verbal information. Such information has been processed through the declarative memory system and stored. It is of interest that semantic memory appears to remain intact over the lifespan and continue to accrue new information even into late life. Semantic memory is often accessed in the performance of new declarative memory tasks, in that information that is previously stored in semantic memory is more easily attended to, encoded, and recalled for short-term use than completely novel information [26].

b) **Implicit memory/Nondeclarative/Procedural memory:** Since Implicit memory is recollected unconsciously, it is called so. It is stored in various regions of the brain like the cerebellum, the neocortex, the striatum, the amygdala, etc [24]. The procedural memory is for motor actions or skills. Procedural memory can be dissociated from episodic memory, in that individuals with amnesia who cannot recall essentially any verbal information can learn and retain procedural skills [27].

Prospective memory: This is the ability to remember to perform tasks in the future, such as performing sequences of functional activities, and other sequential tasks requiring timing and performance of tasks at specific time periods. Prospective memory operates in two different formats: event-based and time-based. Event-based prospective memories consist of responses that are triggered by a stimulus. Time-based procedural memories are triggered by specific times. Prospective memory is implicated in a variety of functional impairments in people with psychiatric conditions [28].

Memory consists of the following steps - encoding, storage, and recall (retrieval). Encoding is the process of altering the material reaching our nervous system into a mode that the system can manage so that it can be easily stored. There are various methods through which knowledge can be encoded via visual, acoustic, and semantic coding. The short-term memory (STM) is encoded mainly via acoustic coding. Long-term memory (LTM), however, usually involves semantic coding. Nonetheless, data in LTM can also be encoded both via visual and acoustic coding. When it comes to acquiring data out of storage, the process of retrieval comes into the picture. Unable to remember information can be due to the inability to retrieve that piece of information. Retrieval helps us understand the dissimilarities among STM and LTM. STM is stored and retrieved chronologically. The storage and retrieval of LTM on the other hand occur via association. Thus, the organization of information can facilitate the process of retrieval [24].

1. **Language skills:** Language and language development are cognitive processes that involve the ability to understand and express thoughts through spoken and written words. Language skills include receptive and productive abilities and the ability to understand language, access semantic memory, identify objects with a name, and to respond to verbal instructions with behavioral acts. Language is further thought to be comprised of interacting subsystems or components: phonology (the system of speech sounds), lexicon (vocabulary), syntax (grammar), semantics (meaning), and pragmatics (social aspects of language that consider the speaker and the context) [29].

   Language skills are assessed with measures of fluency, object naming, and responding to instructions. Language abilities can be impaired in neuropsychiatric conditions but are much more commonly impaired in conditions involving brain damage, stroke, or degenerative dementia [30].

1. **Attention:** Attention is a cognitive process that allows people to focus on a specific stimulus in the environment. Attention and concentration are a multifaceted construct and are generally divided into two global subdomains: selective attention and sustained attention (or vigilance). Concentration would generally fall under the rubric of sustained attention [31].

2. **Sensation and perception:** Sensation refers to the ability of a person to detect a stimulus that occurs in one of the five sensory modalities (visual, auditory, tactile (touch), olfactory (smell), and gustatory (taste)). Perception is a cognitive process that allows people to take in information through their senses (sensation) and then utilize this information to respond and interact with the world. In the domain of perception, sensory information is processed and integrated. One of the concepts of perception is the identification of previously experienced objects from sensory information. Perception can be assessed in terms of the ability to recognize objects, sounds, and for the intactness of the perceptual fields [6].

3. **Executive functions:** Broadly defined, executive functions include initiation, motivation, planning, and control of goal-oriented basic and complex actions, and incorporate more basic executive processes such as shifting, updating, and inhibition. Various long-term memory systems allow information to be retained over weeks, months, and even years. Memory systems are specialized for different types of information (facts, events, and procedures) [7].

4. **Social cognition:** Social cognition is defined as the ability to understand another person's behavior or mental state through the analysis of a wide range of perceptual cues, mainly including facial expression, eye gaze, body posture, and other sociolinguistic parameters. It is essential to produce appropriate behaviors in the context of interpersonal situations and is unsurprisingly disrupted in a vast range of neurological or neurodevelopmental conditions marked by both communicational difficulties and abnormal behaviors such as, without being exhaustive, schizophrenia, autism spectrum disorders, or fronto-temporal dementia [32]. Social cognition is a set of complex cognitive processes centered on social interactions, such as understanding other persons' wishes and needs. Related to social cognition is metacognition, which refers to the ability to reflect upon one's own cognitive processes [7].

Physiological Mechanisms of Cognition

Neurobiological Basis of Cognition: Cognition fundamentally controls thoughts and behaviors, and these are regulated by discrete brain circuits which are underpinned by several neurotransmitter systems. There are several brain chemicals which play major roles in regulating cognitive processes: including dopamine, noradrenaline (norepinephrine), serotonin, acetylcholine, glutamate, and gamma Aminobutyric acid (GABA). Although the degree of complexity in the prefrontal cortex is significantly different between humans, non-human primates, and rodents, there is sufficient homology in the neuroanatomical and neurochemical circuitry between the species to allow for a general description of the circuitry of the prefrontal cortex [33].

The hippocampal formation, an important brain structure involved in learning and memory and in emotions, appears to be particularly affected by plastic processes throughout the lifespan of mammals, including humans. Among the most remarkable forms of neural plasticity is the ability of the hippocampus to continuously generate functional neurons during adulthood, a highly regulated process known as adult hippocampal neurogenesis, which is integral for the hippocampus functions [34].

Besides structural plasticity, the hippocampus can exhibit the form of functional synaptic plasticity known as long-term potentiation, which is widely believed to be one of the main neural mechanisms by which memory is stored in the brain. Therefore, the extended restructuring and functional remodeling of the hippocampus, according to experiential stimuli and diverse endogenous and exogenous factors, may confer important adaptive plasticity [35].

On the other hand, the perpetual capacity for structural changes might render the hippocampus particularly sensitive to perturbations that may have adverse consequences on hippocampal function. Indeed, the hippocampus is a vulnerable structure impaired by events, such as stroke, head trauma, and epilepsy, and it is susceptible to damage during aging and repeated stress. Plastic changes triggered by intense and prolonged negative stimuli could be responsible for disease progression; this aspect of neural plasticity could be referred to as maladaptive [36].

Influence of Physiological Parameters and Metabolic Hormones on Cognitive Performance: Cognitive performance is based on brain functions, which have energetic demands. Cognition is a function of the central nervous system, which consumes a significant amount of energy. For example, in humans, 20% of the resting metabolic rate is due to the metabolic costs of the brain even though it represents only 2% of the body mass. The generation and propagation of neural signals increase energy consumption, because of the energetic costs of neurotransmitter synthesis and the activity of the Na+/K+ pumps, both of which use ATP [37]. Further, the storage of information requires additional neural tissue, either in numbers of neurons or in numbers of connections between these neurons, which increases the energetic demands of the brain [38].

Cognitive performance is modulated by physiological parameters such as metabolic hormones. Physiological mechanisms of cognition have been well studied in the laboratory, but rarely under natural field conditions. So, more research is needed on the influence of natural variation in

blood glucose levels on cognitive performance. They also found that seasonal changes in hormone secretion might have pronounced effects on cognitive performance [39].

These physiological parameters include:

(1) **Blood glucose levels:** Glucose is the most important energy source for the brain, which is the organ where cognitive processes occur. Increased cognitive demands were shown to induce accelerated absorption of glucose from the blood in the brain of humans and rats [40]. By contrast, nothing is known about the influence of reduced blood glucose levels on cognitive performance. This may be related to the fact that the supply of glucose to the brain remains relatively constant even when blood glucose levels are decreasing. This is achieved via the Glucose transporter 3 (GLUT3), which occurs only in the brain. GLUT3 allows a constant uptake of glucose from the blood relatively independent of blood glucose level. However, if blood glucose levels fall below 5 mM (mmol/l) in humans, then glucose uptake in the brain by GLUT3 decreases. As the GLUT3 transporter is important for brain metabolism in all mammals and is well studied in laboratory rodents [41].

Glycemic Extremes: The relationship between glycemic extremes (i.e., hypoglycemia and hyperglycemia) and cognitive functioning remains controversial. There was no evidence of greater cognitive decline associated with incident severe hypoglycemic episodes, and other studies have also failed to find an association between a history of severe hypoglycemic events and cognitive functioning [42]. However, there is an apparent link between hypoglycemia and cognitive impairment in older adults with type 2 diabetes, and a case-control study found that older adults with type 1 diabetes who had recent severe hypoglycemic events had poorer cognitive functioning than those who had not had an event in the past 3 years. Thus, the neurological effects of severe hypoglycemia may be greatest during early development and during age-associated neurodegeneration [43].

(2) **Stress hormones:** Exposure to acute stress induces the release of metabolic hormones, which have a secondary effect on cognition via the regulation of blood glucose levels in three consecutive phases [44] (Figure 2).

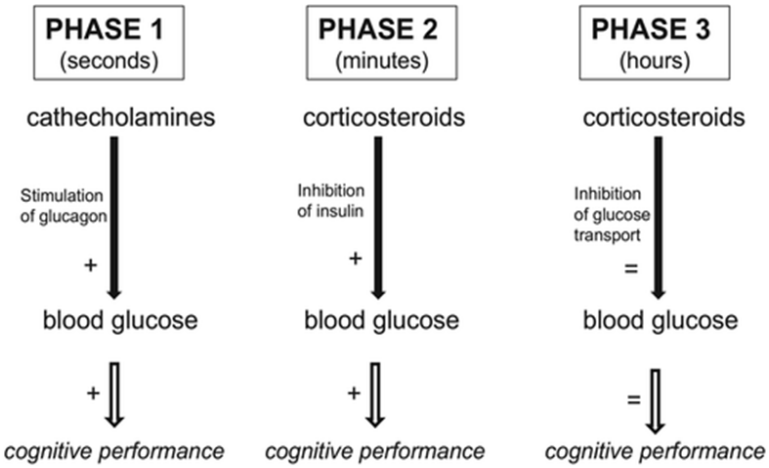

Figure (2): Physiological responses to acute stress affect glucose metabolism in three successive phases. Phase 1 (sympathetic arousal, lasting seconds): catecholamines such as adrenaline stimulate glucagon secretion, which induces an increase in blood glucose levels.

Phase 2 (beginning of the delayed stress response, lasting minutes): corticosteroids inhibit both the secretion and the transport of insulin, which induces an increase in blood glucose levels by decreased glucose uptake. Phase 3 (end of the delayed stress response, lasting hours): corticosteroids inhibit the transport and utilization of peripheral glucose, which induces stabilization of blood glucose levels at normal concentrations. Black arrows represent hormonal influences on blood glucose levels. White arrows represent effects of blood glucose levels on cognitive performance. [39]

• **Corticosteroids hormones:** The effects of corticosteroids on cognition are centered in the hippocampus, a brain region containing large concentrations of both mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). MRs have a tenfold higher affinity for corticosterone than GRs. Because of the differential activation of MRs and GRs (known as the Yerkes–Dodson law), corticosteroids have a dose-dependent biphasic effect on cognition, i.e., an inverted U-shaped relationship. At low doses, corticosteroids (mainly bound to MRs) stimulate synaptic plasticity and hippocampal excitability through long-term potentiation of neurons [39]. However, at high doses, corticosteroids (equally bound to MRs and GRs) have negative effects on cerebral functions, disrupting synaptic plasticity and blunting hippocampal excitability. Cognitive performance for spatial learning and aversive learning was impaired in rats injected with high concentrations of corticosterone [45]. Stress levels of GCs facilitate hippocampal-dependent memory under highly aversive conditions while impairing memory under less aversive conditions [46]. This dose-dependent system is thought to enable the brain to distinguish between circadian rhythms (corticosteroid levels increase at the beginning of the activity period each day) and stress-dependent release of corticosteroids, enabling adaptive changes in information processing in unpredictable environments [39].

(3) **Other hormonal influences:** Gonadal steroids affect cognition through the modulation of neurotransmitter production and release. Testosterone stimulates the cholinergic system in the hippocampus of male rats. Gonadal steroids have been shown to improve hippocampal synaptic plasticity by increasing dendritic density and neuronal potentiation. Physiological doses of testosterone and estradiol improve cognition in mammals [47]. Cognitive performance for spatial learning, aversive learning, and object recognition improved in gonadectomized male rats injected with testosterone. In human and non-human primates, a positive correlation was found between visuo-spatial attention and both testosterone levels and estradiol levels. In contrast to physiological doses, very high or chronic doses of testosterone can impair cognition in male mammals, for example, spatial learning in rats or associative learning in macaques. Similarly, in females, high estradiol levels impair spatial reference memory in rats [39].

Other hormones might affect cognition, including neuropeptides such as endorphin and vasopressin that are released both peripherally and centrally in response to stressors. Some studies suggest that endorphin and vasopressin have an impairing effect on cognition. However, vasopressin has also been reported to have an enhancing effect on aversive learning and spatial learning [48]. Vasopressin secretion changes seasonally, being higher during periods of low water availability, due to its important role in osmoregulation [49].

Diabetes mellitus (DM) is a major global health problem not only because of its high and growing prevalence, which has tripled in the last 20 years, but also because of the number of

premature deaths it causes. DM is a multifactorial disease triggered by a combination of genetic, epigenetic, and environmental factors. The increase in life expectancy and unhealthy lifestyle habits, such as a sedentary lifestyle and the consumption of foods rich in saturated fats and added sugars, are risk factors for the development of obesity and associated comorbidities, such as metabolic syndrome, also called insulin resistance syndrome [50].

Classification of Diabetes Mellitus: DM can be classified into four general categories: type 1 DM (DM-1), type 2 DM (DM-2), gestational DM, and a group of specific types of DM due to other causes including monogenic DM syndromes, diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced DM (such as post-transplantation DM). DM-1 and DM-2 are the most common forms of disease [51]. Diabetes mellitus is a complex metabolic disease with a rapidly rising incidence rate that tends to affect younger populations. Patients with type 1 DM (T1DM), which occurs more commonly in adolescents, experience β-cell destruction in the pancreatic islets, insulin production loss, and elevated blood glucose, eventually leading to devastating effects in multiple organs [52]. Patients with type 2 DM (T2DM) suffer from obesity and insulin secretion dysfunction, resulting from insulin resistance [53].

Chemical-Induced DM Rat Models: Several chemical compounds have been shown to be able to induce DM in animal models, and the two most widely used diabetogenic agents are alloxan and streptozotocin (STZ). Both are cytotoxic glucose analogues that bind to pancreatic β-cell GLUT-2 transporters causing irreversible damage, leading to hyperglycemia, β-cell necrosis, and weight loss, without causing damage to other organs. These diabetogenic agents are very unstable, so the preparations must be prepared at the time they are injected (half-life: alloxan, 1–2 min; STZ, 1 h) [54]. The main advantage of the chemically induced models is that they are simple and relatively cheap. In addition, following different protocols of the time of induction, route of administration, and dose, it is possible to induce DM-1 or DM-2 [55]. The main disadvantages of these models are (a) that human DM is rarely caused by a toxic substance; (b) the possibility that these compounds can cause toxicity in the liver and tubular cells where GLUT-2 is expressed; and (c) that a single dose can cause mortality due to ketosis associated with acute damage [50].

Two classical chemical agents, STZ and alloxan, selectively damage β-cells, resulting in diabetic rodent models. The alloxan-induced model is characterized by a multiphase blood glucose response and a high animal mortality rate due to a high level of ketoacidosis. Compared with alloxan, STZ has a longer half-life; thus, it is stabler and more suitable for long-term research. In their study, they used continuous low-dose i.p. STZ injections to establish a T1DM model [56].

STZ is an N-nitroso derivative of glucosamine that was found in *Streptomyces acromogenes* (a soil microorganism) and has broad-spectrum antibiotic potential [57]. STZ injections are widely used to induce T1DM or T2DM models. STZ selectively enters β-cells in pancreatic islets via the glucose transporter GLUT2, forming diazomethane and causing DNA strand breaks in these cells, resulting in β-cell death. A low dose of STZ combined with a high sugar diet is the most used paradigm for inducing T2DM in rodents, while a continuous low dose of STZ intraperitoneally or intravenously (i.p. or i.v.) injected can induce T1DM [53].

Streptozotocin and Cognition: STZ impairs memory in rats through altering the central nervous systems (CNS) as a result of impaired cholinergic dysfunction, oxidative stress, persistent hyperglycemia, and alterations in the glucagon-like peptide (GLP) [58]. Pathology analysis revealed STZ-induced neuron loss in a dose-dependent manner, both in the cortex and in the hippocampus, as evidenced by a significantly decreased neuronal number in the cohort treated with 75μg of STZ/mouse. Previous studies indicated that a low dose (25μ g/mouse) of STZ impaired neural plasticity; at a higher dose of 75μ g/mouse STZ, further long-term potentiation deficits were noted along with induced neuronal loss in both the cortex and the hippocampus, which could be considered a possible mild cognitive impairment (MCI) or pre-MCI animal model; and finally, at 150μ g/mouse STZ, dementia was induced, feasibly indicating a state of Alzheimer's disease [59].

STZ-induced mice anxiety-like behavior, as well as impaired working memory and spatial memory. Previous studies found that the T1DM model had significant memory loss [60]. Moreover, DM mice exhibited deteriorated short-term memory and spatial memory, even after a short period after STZ injection (22nd day) [61], whereas their data confirmed that impaired cognition and memory loss were still exhibited long after STZ injection. Meanwhile, during the feeding process, they found that the mice had high blood glucose and urine sugar after 20 weeks of STZ injection, suggesting possible long-term hyperglycemia, permanent memory impairment, and irreversible synaptic link loss. This study complemented the results of long-term effects of STZ injection [53].

Pathophysiology of Diabetes-Induced Complications: DM is characterized by impaired insulin secretion or utilization, accompanied by hyperglycemia and glycosuria. These disruptions progress gradually and arise mostly due to the adverse effects of hyperglycemia and its associated metabolic anomalies on the normal structure and functioning of micro- and microvasculature. The structural and functional disruptions in organ system vasculature led to micro- and macrovascular complications such as cardiovascular diseases (e.g., heart attack and stroke), neurological disorders (e.g., cognitive impairment, dementia, and depression), nephropathy, retinopathy, obesity, and some cancers. Therefore, DM remains one of the greatest public health challenges worldwide [62]. DM is regarded as a prevalent metabolic illness that has a negative influence on people's quality of life. Brain atrophy and cognitive decline are two neurological problems that are recurrently seen in the CNS and peripheral system [63, 64].

Additionally, there is growing evidence that DM causes memory loss and cognitive dysfunction in DM animal models. Although the precise mechanism is unknown, a major risk factor for cognitive decline is DM. The hippocampus is a crucial part of the brain that regulates learning and memory, and it has been shown that chronic hyperglycemia can cause ultrastructural destruction of the hippocampus [65]. There are several things that seem to contribute to cognitive decline in diabetics. Many investigations have shown that hyperlipidemia and persistent hyperglycemia are important initiating and developing factors for diabetes-related cognitive impairments. Additionally, deposition of amyloid-β (Aβ), aberrant insulin signaling, and a strong inflammatory reaction can all result from a disruption of protein, carbohydrate, and lipid metabolism under diabetic conditions, which also contributes to diabetes-related neuronal injury and cognitive deficiencies [58,66].

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