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Review article

Pathogenetic pathways of cognitive dysfunction and dementia in metabolic syndrome

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ABSTRACT

The prevalence of dementia worldwide is growing at an alarming rate. A number of studies and meta-analyses have provided evidence for increased risk of dementia in patients with metabolic syndrome (MS) as compared to persons without MS. However, there are some reports demonstrating a lack of association between MS and increased dementia risk. In this review, taking into account the potential role of individual MS components in the pathogenesis of MS-related cognitive dysfunction, we considered the underlying mechanisms in arterial hypertension, diabetes mellitus, dyslipidemia, and obesity. The pathogenesis of dementia in MS is multifactorial, involving both vascular injury and non-ischemic neuronal death due to neurodegeneration. Neurodegenerative and ischemic lesions do not simply coexist in the brain due to independent evolution, but rather exacerbate each other, leading to more severe consequences for cognition than would either pathology alone. In addition to universal mechanisms of cognitive dysfunction shared by all MS components, other pathogenetic pathways leading to cognitive deficits and dementia, which are specific for each component, also play a role. Examples of such component-specific pathogenetic pathways include central insulin resistance and hypoglycemia in diabetes, neuroinflammation and adipokine imbalance in obesity, as well as arteriolosclerosis and lipohyalinosis in arterial hypertension. A more detailed understanding of cognitive disorders based on the recognition of underlying molecular mechanisms will aid in the development of new methods for prevention and treatment of devastating cognitive problems in MS.

1. Introduction

The prevalence of dementia worldwide is growing at an alarming rate. Globally, the number of patients with dementia was estimated to be 36 million in 2010; this number is anticipated to triple by 2050 [1,2]. The total cost of dementia was $948 billion in 2016, with an annual increase of 15.9% for the period 2000–2016, indicating the grave economic burden associated with this pathology [3].

The two most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (VD), which can coexist in the same patient. According to some estimates, at least 50% of patients with dementia have cerebral vascular lesions, accompanied by various signs of neurodegeneration [4]. VD is an umbrella concept, encompassing different cardiac and/or vascular disorders capable of inducing cognitive deficits [5]. The causes of VD include chronic heart failure, cardiac arrest, carotid artery stenosis resulting in chronic hemispheric hypoperfusion, ischemic or hemorrhagic stroke, cerebral vasculitides, as well as hereditary and sporadic cerebral small vessel disease [4].

Metabolic syndrome (MS) is a major cardiovascular risk factor classically involving four components: obesity, dyslipidemia, arterial hypertension (AH), and diabetes mellitus (DM). A number of population-based epidemiological studies and meta-analyses provide evidence for increased risk of all-cause dementia [6], AD [7,8], and VD [9,10] in patients with MS, compared to persons without MS. However, there are also some reports demonstrating a lack of association between MS and increased risk of dementia [11–13]. This controversy might be ascribed to the variability in the criteria used to define MS, different approaches used for the assessment of cognitive function, different follow-up periods, and the presence of yet unidentified confounding factors. Investigations of the association between MS and cognitive impairment, both of which are complex, multifactorial disorders, are complicated by marked heterogeneity of clinical manifestations and different predominant pathogenetic pathways. Therefore, the problem of causal relationship between MS and dementia remains unresolved. Yet, a

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detailed analysis of known pathophysiological mechanisms underlying the development of functional and structural disorders in the brain due to MS could contribute to the identification of novel therapeutic targets.

Thus, in this review, we took into account the potential role of individual MS components in the pathogenesis of MS-related cognitive impairment; we thus considered the injurious effects of AH, DM, atherogenic dyslipidemia, and obesity on cognitive function. Given the broad scope of this review, we apologize to all researchers to whose original contributions we could only refer via reviews by others.

2. Arterial hypertension and cognitive dysfunction

AH is now considered one of the major risk factors for VD [14,15]. Early functional disorders of cerebral blood flow in AH include a reduced functional hyperemic response [16] and rightward shift of the cerebral autoregulation curve with an increase in the lower threshold of autoregulation, which leads to increased risk of cerebral hypoperfusion during ischemia and episodes of systemic hypotension [17].

Beason-Held et al. [18] analyzed the regional cerebral blood flow in hypertensive versus normotensive persons, using positron emission tomography (PET), over a period of 7 years. In normotensive subjects, blood flow at the end of the observation period was significantly elevated in certain brain areas, while it was decreased in the others, which is considered to reflect the normal age-dependent dynamics of brain perfusion. Age-dependent regional cerebral blood flow decrease has been found to be more pronounced in hypertensive individuals than in normotensive controls, and the normal age-related augmentation of cerebral blood flow in other areas was mitigated in patients with AH.

2.1. Hypertension-induced structural changes in cerebral arteries and in the neurons

Untreated AH results in well-characterized structural changes in brain arteries, referred to as vascular remodeling. In particular, increased tangential stress on the arterial wall stimulates both hypertrophy and proliferation of vascular smooth muscle cells, which, in turn, causes increased arterial wall thickness and wall surface-to-lumen surface ratio, as well as decreased lumen diameter [19]. These changes in vascular geometry result in increased hydrodynamic resistance and enhanced responsiveness to vasoconstrictors. Along with rarefication of brain capillaries, the above-mentioned AH-induced structural changes in arteries culminate in chronic cerebral hypoperfusion.

Using experimental models of AH, Flores et al. [20] studied early structural changes in the neurons belonging to cerebral areas critical for the regulation of cognitive function, such as the prefrontal cortex, CA1 hippocampal area, and nucleus accumbens. The most significant neuronal changes in these areas included decreased dendritic length and reduced dendritic spine density, which may impair synaptic communication between neurons, a process critically involved in the maintenance of normal cognitive performance.

2.2. Pathogenetic scenarios of vascular dementia in hypertension

AH can contribute to the development of cognitive dysfunction and VD by means of several mechanisms (Fig. 1). Firstly, decompensated, long-standing AH is one of the main causes of chronic heart failure, which might be associated with encephalopathy because of global cerebral hypoperfusion [21,22]. Secondly, brain tissue injury may develop due to atherothrombosis of carotid or intracranial arteries, because AH results in marked endothelial dysfunction in the elastic arteries and, therefore, increases the risk of atherosclerosis. Atherothrombotic occlusion of major cerebral arteries causes ischemic stroke, followed by the development of post-stroke dementia in approximately a quarter of cases [23]. Thirdly, cerebral small vessel disease (SVD) affects mainly the white matter [24].

2.3. Cerebral small vessel disease in hypertension

At the morphological level, SVD is manifested by pronounced wall thickening in the penetrating arteries and parenchymal arterioles, with critical reduction in their lumen diameter. After originating from pial arteries coursing over the surface of the brain, penetrating arteries dive into the brain tissue, where they become parenchymal arterioles and then branch further, forming capillaries.

The neuroimaging hallmarks of SVD comprise leukoaraiosis, white matter hyperintensities, lacunar infarcts, microinfarcts, and dilated perivascular spaces [25,26]. Degenerative changes in the walls of the smallest cerebral vessels can also result in microbleeds, which are currently detected using high-field magnetic resonance imaging (MRI) [27]. Given the anatomical characteristics of the cerebral arterial supply, the subcortical white matter at the boundary between vascular territories supplied by the middle and anterior cerebral arteries is particularly susceptible to injury in SVD [15]. The process of irreversible neuronal injury in clinical cerebral SVD can be quantified using advanced MRI-based analysis. The annual rate of brain atrophy in healthy sexagenarians was estimated to be approximately 0.5%, while it was 2-fold higher in patients with SVD [28].

Recent clinical studies have provided solid evidence linking cognitive dysfunction in patients with AH to the progression of periventricular and deep white matter injury, defined as white matter hyperintensities on MRI [29]. AH-related white matter injury is initialized by endothelial dysfunction associated with diminished cerebral vasoreactivity and flow-mediated vasodilation [30]. Brain tissue hypoxia resulting from both structural arterial remodeling and impaired regulation of vascular tone leads to increased blood–brain barrier (BBB) permeability [31]. Consequently, plasma proteins, such as fibrinogen and immunoglobulins, egress from the circulation, accumulating in the vessel wall, which induces an inflammatory response by activation of microglia and astrocytes [32]. Activated neuroglial cells produce proinflammatory cytokines, which are able to activate oligodendrocyte precursors, which in turn produce excessive amounts of matrix metalloprotease 9 [33]. The latter damages BBB junctional proteins, thereby perpetuating the vicious circle and further increasing BBB permeability. Plasma protein infiltration of the wall of the smallest cerebral arteries and arterioles causes progressive loss of vascular smooth muscle cells and their substitution by fibrohyaline deposits. From a morphological viewpoint, these changes are characterized as arteriolosclerosis [34]. Arteriolosclerosis affects cerebral arterioles with a diameter of 40–150 μm and in principle can be observed not only in the brain, but also in other organs, e.g., in the kidney [35].

The more advanced vascular wall changes, characterized by the loss of integrity of the internal elastic membrane and massive hyaline deposition in the media, are referred to as lipohyalinosis. In some cases, the process advances further, resulting in segmental necrosis of the wall of a penetrating artery, with intensive perivascular accumulation of leukocytes and near-total luminal obstruction [36]. This extreme type of hypertension-associated small artery injury is called fibrinoid necrosis.

White matter injuries such as leukoaraiosis and white matter hyperintensities likely involve the process of axonal demyelination, leading to decreased velocity of action potential transmission, axonal injury, and ultimately axonal loss. Chronic cerebral hypoxia has been associated with oligodendrocyte dysfunction and hence impaired maintenance of the myelin sheath [37]. Although signs of remyelination have been consistently observed in white matter lesions [38], this process is largely ineffective, potentially because of the hypoxic injury to oligodendrocyte progenitor cells [39] and/or their developmental arrest [40,41].

2.4. Clinical evidence of cognitive dysfunction in hypertension

The existence of a causal relationship between AH and cognitive

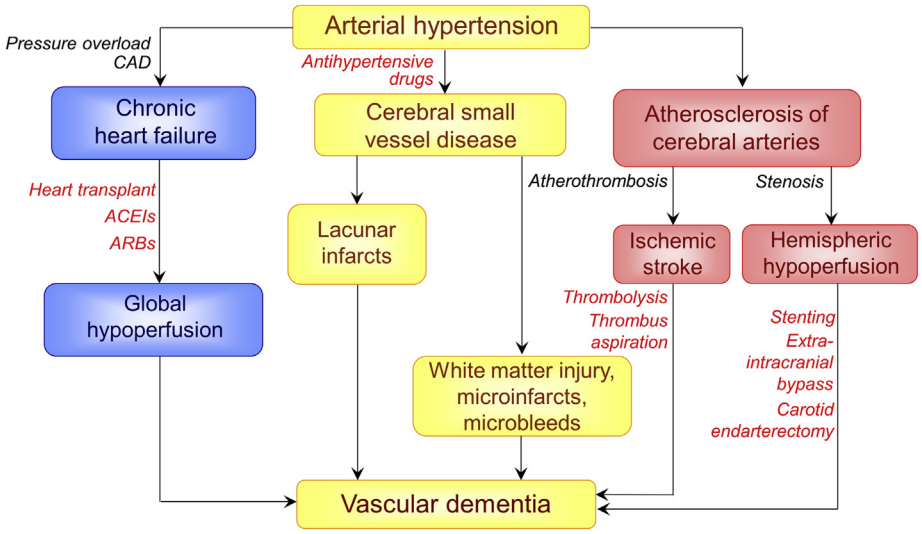

Fig. 1. Pathogenetic scenarios of cognitive dysfunction and vascular dementia in arterial hypertension. Hypertension can increase the risk of vascular dementia through several mechanisms. Firstly, chronic pressure overload along with coronary artery disease results in heart failure, which is associated with encephalopathy due to global cerebral hypoperfusion. Secondly, hypertension causes small vessel disease leading to lacunes, white matter injury, microinfarcts, and microbleeds. Thirdly, hypertension is known risk factor of cerebral atherosclerosis, which manifests by ischemic stroke or chronic hemispheric hypoperfusion. Therapeutic and surgical interventions aiming prevention of dementia are also shown (in red italics). ACEIs – angiotensin-converting enzyme inhibitors; ARBs – angiotensin II receptor blockers; CAD – coronary artery disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

dysfunction is supported by the results of interventional clinical trials investigating the effects of antihypertensive therapy on the extent of cognitive deficit. For example, a large network meta-analysis was reported by Marpillat et al. [42]; this study comprised 19 randomized clinical trials (n = 18,515) on the effect of antihypertensive drug therapy on cognitive function, and 11 observational trials (n = 831,674) studying the influence of antihypertensive therapy on the risk of dementia. Irrespective of drug combination, antihypertensive therapy improved cognitive functions except language domain. It was also shown that treatment of AH decreases the risk of dementia by 9%. However, this result was only significant when the data obtained in randomized and observational studies were combined. Finally, among different antihypertensive drugs, angiotensin II receptor blockers were found to be superior to other drugs in terms of improvement of cognitive function. Angiotensin II receptor blockers were followed by β-adrenoreceptor blockers, diuretics, and angiotensin-converting enzyme inhibitors. Recent clinical study by SPRINT MIND investigators have shown that among adult patients with AH, intensive blood pressure control have not resulted in a significant reduction in the risk of probable dementia but lowered the risk of mild cognitive impairment [43].

Thus, the main pathogenetic factors underlying white matter injury and dementia in AH include endothelial dysfunction, cerebral hypoperfusion, increased BBB permeability, axonal demyelination with failing remyelination, neuroinflammation, and neuronal death. Pharmacological targeting of these mechanisms may give rise to the development of new promising approaches for preventing cognitive dysfunction in patients with AH.

3. Atherogenic dyslipidemia and cognitive impairment

Atherogenic dyslipidemia, usually defined as hypertriglyceridemia and decreased high-density lipoprotein cholesterol, is a key MS component. Dyslipidemia typically contributes to the development of atherosclerotic lesions both in carotid and vertebrobasilar systems. Moderate to severe arterial stenosis is associated with chronic hemispheric hypoperfusion, while plaque destabilization with intervening thrombosis can result in (sub)total occlusion and classic ischemic stroke. A few months after ischemic stroke, dementia develops in nearly 20% of cases [23]. One year after stroke, the incidence of dementia has been estimated to be about 3% per year [44]. The probability of post-stroke dementia development critically depends on the location of the ischemic area in the brain. Even small infarcts may pose a significant risk of dementia if they are located in specific brain areas that are heavily involved in cognitive performance. Ischemic stroke in the vascular territory supplying such an area is called a strategic infarct [45]. Using voxel-based morphometry analysis of brain MRI images, Zhao et al. [46] provided exact mapping of strategic brain areas related to dysfunction of particular cognitive domains (e.g., memory, language, attention, etc.). Ischemic stroke cases involving the left angular gyrus, left basal ganglia structures, and the white matter around the left basal ganglia are most commonly associated with dementia. Recently, the Meta VCI Map consortium announced a new project aiming to perform meta-analyses on identifying strategic lesion locations for vascular cognitive impairment using lesion–symptom mapping [47].

Atherosclerotic lesions can also occur in smaller cerebral arteries, such as penetrating arteries. Small plaque can either occlude the origin of the penetrating artery or extend into the lumen of the penetrator, or appear as microatheroma solely within the penetrating artery [48,49]. While atherosclerosis typically affects elastic arteries, penetrating arteries seem to be an important exception, representing an example of the smallest artery still demonstrating typical atheromatous lesions containing a lipid core and fibrous cap. Since penetrating arteries lack anastomotic connections with other vessels, its permanent occlusion will inevitably cause necrosis of the vascularized region. Atherosclerotic or embolic occlusion of the penetrating arteries results in lacunar infarcts in the basal ganglia, pons, or thalamus. On histopathological examination, old lacunar infarcts appear as round or elliptic, fluid-filled cavities of 3–15 mm in diameter located in subcortical brain areas, each corresponding to the vascular territory of a single penetrating artery [50]. In contrast to dilated perivascular spaces, the presence of multiple lacunar infarcts has been found to predict the development of cognitive decline in patients with cerebral SVD [51]. Modern neuroimaging modalities demonstrate spatial resolution sufficient for quantitative assessment of penetrating artery lesions. For example, three-dimensional (3D) reconstruction of lenticulostriate arteries using high-field (7 -T) MRI demonstrated a decreased number of arteries in the basal ganglia in patients with lacunar strokes versus healthy controls, which is suggestive of atheromatous arterial occlusion [52]. With 3D image analysis and modeling of vessels, it is even possible to identify the individual lenticulostriate artery associated with a specific lacunar infarct.

4. Diabetes mellitus and cognitive dysfunction

Epidemiological studies have clearly demonstrated that the incidence of dementia is significantly higher in patients with DM, particularly in persons older than 65 years [53,54]. The rate of age-related cognitive decline in patients with DM was 2-fold higher than in persons without the disease over the same period of time [55]. However, the

presence of a causal relationship between DM and cognitive dysfunction has been questioned in recent population-based studies, because the existing association between these entities can be attributed to differences in socioeconomic status, educational level, and baseline cognitive performance in childhood [56].

Patients with DM demonstrate the whole spectrum of cognitive disorders, from subjective cognitive complaints to mild cognitive impairment and overt dementia. It is unknown at present whether these entities represent separate stages of the entire cognitive dysfunction continuum or whether they rather develop independently, based on distinct mechanisms. Pathogenetic pathways of dementia development in DM include both vascular injury and neurodegeneration, because the risk of AD in patients with DM was found to be significantly higher, even after correction for vascular disease, than in those without DM [53]. The risk factors of dementia in patients with DM include poor glycemic control, as assessed by the level of glycated hemoglobin [57], variability in the blood glucose level, and the duration of disease [58]. Increased risk of dementia was also observed in the patients with DM having manifestations of diabetic microangiopathy (e.g., retinopathy) and macroangiopathy (e.g., myocardial infarction or stroke) [59].

Current neuroimaging techniques are useful for the identification of subtle structural and functional abnormalities correlating with the onset of cognitive deficit. Examples are global cerebral atrophy on conventional MRI [60], generalized microstructural alterations of white matter, including changes in the connectome revealed with diffusion-tensor MRI, and decreased task-related brain activation on functional MRI [61]. DM is associated with a significantly increased number of lacunar strokes and white matter hyperintensity areas [62]. The above-mentioned structural abnormalities in the brain were described in the prediabetic adults having insulin resistance, without overt diabetes, which suggests that the main driver of cognitive dysfunction in DM is impaired insulin signaling, rather than chronic hyperglycemia [62]. The presence of cerebral SVD in DM is confirmed by neuropathological data demonstrating more extensive cerebrovascular pathology in patients with DM than in individuals without DM [63].

4.1. Mechanisms of cognitive dysfunction in diabetes mellitus

There are three groups of mechanisms implicated in the occurrence of cognitive dysfunction in DM (Fig. 2): i) vascular cerebral injury at the level of major arteries or small vessels, ii) potentiation of a neurodegenerative cascade typical of that in AD, that is, amyloid deposition and tau hyperphosphorylation, iii) development of neurodegenerative process that is not related to classical mechanisms established in AD [64].

The mechanisms of cerebral vascular injury, including SVD, have been discussed above; however, it is important to note that DM represents an important additional risk factor for SVD. DM is associated with substantial endothelial injury caused by advanced glycation end-products, toxic lipids, and protein aggregates. Plasma protein accumulation in the vessel wall can also contribute to endothelial dysfunction, augmented generation of reactive oxygen species, and reduced production of endothelium-derived vasodilators. Both direct endothelial injury and reactive oxygen species-mediated effects can increase BBB permeability and increase the activity of matrix metalloproteases, which, in turn, initiate the process of axonal demyelination in the brain [65].

4.2. Neurodegeneration in diabetes mellitus

In the setting of DM, the mechanisms underlying AD could be potentiated by means of central insulin resistance. It has been shown experimentally that impaired neuronal insulin signaling results in increased cerebral amyloid-β deposition [66] and tau hyperphosphorylation [67,68]. Accumulation of amyloid-β in the brain in patients with DM can be due, at least in part, because of its impaired degradation by specific proteases, such as neprilysin, insulin-degrading enzyme, and endothelin-converting enzyme [69]. Under conditions of central insulin resistance, increased neuronal accumulation of autophagosomes carrying the amyloid-generating enzymes β-secretase 1 and γ-secretase has also been demonstrated in a murine model of DM [70]. This is consistent with the data showing that normalization of neuronal sensitivity to insulin and restoration of insulin signaling in hippocampal neurons attenuated cognitive dysfunction in patients with coexisting DM and AD [71].

Taking into account the complexity of the interaction between DM and both clinical and neuropathological manifestations of AD, studies have recently switched the focus to putative neurodegeneration mechanisms, which are not related to the formation of amyloid plaques or neurofibrillary tangles. The mechanisms underlying non-ischemic neuronal death in DM may involve advanced oxidative injury of the neuronal membrane [72], systemic mitochondrial dysfunction [73], posttranslational modification of calcium-dependent protein kinases [74], as well as disorders of both synthesis and metabolism of amylin. Amylin is polypeptide hormone, which is secreted by pancreatic β-cells along with insulin. Amylin plays an important role in glucose homeostasis, suppressing the release of glucagon from α-cells and decreasing blood glucose level [75]. Human but not rodent amylin is amyloidogenic. It is prone to aggregate in case of hyperexpression, which is observed in prediabetes, because hyperinsulinemia is always associated

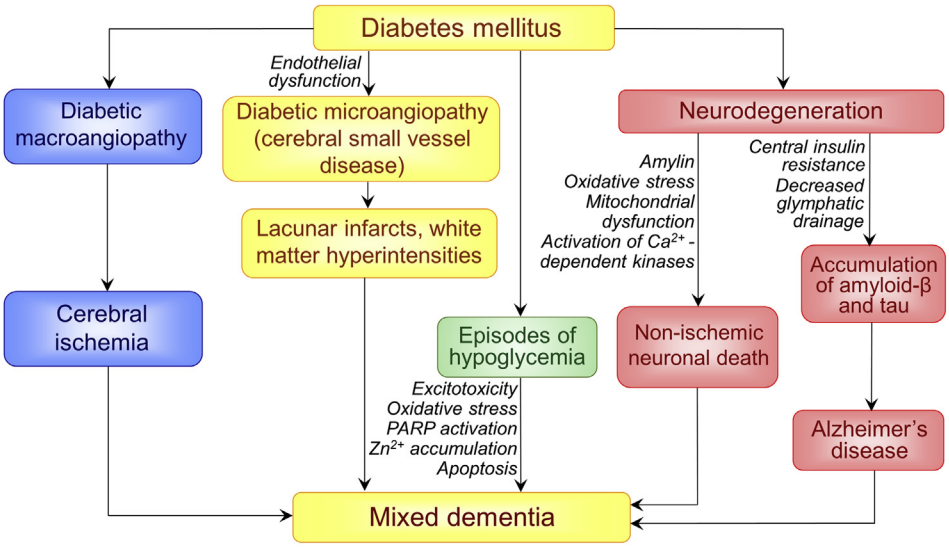

Fig. 2. Pathogenetic pathways leading to mixed dementia in diabetes mellitus. There are five major pathways of dementia development in diabetes: i) diabetes results in accelerated atherosclerotic injury of major cerebral arteries, which causes acute or chronic ischemia; ii) diabetic microangiopathy affects cerebral small vessels causing lacunar infarcts and white matter injuries; iii) acute episodes of hypoglycemia lead to neuronal death by means of several mechanisms; iv) diabetes promotes Alzheimer's disease; v) non-Alzheimer's neurodegeneration can be also involved. Molecular mechanisms of neuronal injury specific for each pathway are shown in italics. PARP - poly (ADP-ribose) polymerase-1.

with hyperamylinemia [76]. Extensive amylin deposits have been identified in pancreatic islets, kidney, and heart of the majority of patients with type 2 DM. Amylin aggregates and co-aggregates of amylin and amyloid-β have been detected in the brains of patients with concurrent DM and AD [77]. Although the cerebral accumulation of typical amyloid-β in DM patients is questionable, it is conceivable that neurodegenerative changes could develop because of the formation of different types of protein aggregates.

4.3. The role of cerebral glymphatic system dysfunction

In the last years, a new pathogenetic concept of cognitive dysfunction in DM, dealing with the impaired function of the cerebral glymphatic system, has been proposed [78]. Glymphatic transport involves aquaporin-4-mediated release of cerebrospinal fluid from perivascular spaces at the level of cerebral penetrating arteries and arterioles, with subsequent convective movement of interstitial fluid containing various metabolites in the direction of perivenous spaces, which reabsorb the excess tissue fluid [79]. The intensity of glymphatic drainage is substantially enhanced during sleep. Therefore, the glymphatic system represents an important mechanism for removal of potentially neurotoxic substances from the brain parenchyma. Impairment of glymphatic system function has been shown to precede cerebral amyloid-β deposition in animal models of AD [80]. These findings provided strong support for the hypothesis that decreased glymphatic transport plays an important role in the pathogenesis of AD. Furthermore, the extent of cognitive dysfunction in rats with chemically induced DM has been shown to correlate with decreased glymphatic drainage of a fluorescent tracer [81].

4.4. Hypoglycemia and cognitive deterioration in diabetes mellitus

Moreover, recurrent episodes of acute hypoglycemia play an important role in the development of cognitive impairment in patients with DM [82]. Severe hypoglycemia results in diffuse neuronal death within specific vulnerable areas of the brain, such as the neocortex, hippocampus, and striatum [83,84]. The mechanisms involved in hypoglycemia-induced neuronal damage are not fully understood, but may include factors such as excitotoxicity [85], oxidative stress [86], poly(ADP-ribose) polymerase-1 activation [87], postsynaptic zinc accumulation [88], and mitochondrial release of pro-apoptotic molecules [89].

Dementia is now recognized as one of the serious complications of DM, albeit with poorly understood mechanisms. There is an urgent need for the development of new methods of identification of DM patients having an increased risk of dementia in order to implement preventive strategies.

5. Obesity-induced cognitive dysfunction

Obesity is generally viewed as an initializing factor in the development of MS. In this regard, its role in dementia occurrence and progression could be considered using two different approaches: i) the role of obesity *per se*, and ii) the role of obesity-associated secondary disorders, such as DM, AH, and atherosclerosis. Since the second aspect was briefly discussed in the previous sections of the review, here we will focus on the effects of isolated obesity on cognitive function and risk of dementia. The presence of obesity in the middle age predicts the development of mild cognitive impairment in a more advanced age after correction for normal cognitive aging [90,91]. A cross-sectional epidemiological study has also demonstrated negative correlation between body mass index and cognitive function, as assessed by means of delayed-recall testing [92].

5.1. Neuroanatomical substrate of cognitive dysfunction in obesity

Both experimental and clinical studies have indicated that obesity is associated with significant functional and structural alterations in the brain. For example, global cerebral volume has been negatively correlated with body mass index in a heterogenous population (n = 114) [93], while in subjects with morbid obesity (body mass index > 39 kg/m^2), region-specific grey matter atrophy has been found to be confined to such brain areas as the postcentral gyrus, frontal lobes, putamen, and medial frontal gyrus [94]. According to voxel-based morphometry of diffusion-tensor MR images of the brain, increased body mass index was associated with decreased white matter integrity, particularly in the midbrain and brainstem [95,96]. However, recent data by Carbine et al. [97] have suggested that white matter integrity is not uniformly decreased in overweight and obese adolescents, with some brain regions (e.g., anterior and orbital frontal corpus callosum, right inferior fronto-occipital fasciculus, the left cingulum, and left corticospinal tract) demonstrating increased integrity in obese versus non-obese subjects.

Among brain structures, the hippocampus is critically important for learning and memory. Decreased hippocampal volume has been observed in adolescents with MS as compared to healthy adolescents, which has been correlated with cognitive function impairment [98]. High-fat diet-induced obesity in rats was accompanied by decreased long-term potentiation, one of the main mechanisms of learning and memory, in the dentate gyrus and CA1 area of the hippocampus [99]. Feeding of the animals with a high-fat diet was also associated with impaired neurogenesis in the dentate gyrus of the hippocampus [100], as well as with decreased hippocampal production of brain-derived neurotrophic factor [101]. Additionally, diet-induced obesity in rats resulted in increased apoptosis of hippocampal neurons [102], with an associated decrease in the weight of the hippocampus [103].

Thus, the neuroanatomical substrate of cognitive dysfunction in obesity is fairly well characterized. It includes mild to moderate atrophy of different brain areas with selective injury to cerebral regions that are crucial to normal cognitive activity. The main hypotheses explaining the mechanisms of neuronal death and cerebral injury in obesity are summarized below.

5.2. Obesity and neurodegeneration

Obesity has been associated with increased risk of both SVD and AD [104]. The mechanisms of increased risk of AD in adiposity not well characterized. To date, it is known that high-fat diet-induced obesity in transgenic mice overexpressing human amyloid precursor protein 695 was associated with increased deposition of amyloid-β in the brain [105]. Similarly, a fat-enriched diet contributed to increased tau phosphorylation in the hippocampus of transgenic THY-Tau22 mice, which was paralleled by their diminished spatial memory performance in the Morris water maze test [106]. These experimental findings are consistent with clinical neuropathological and biochemical data. For instance, hippocampal expression of AD markers, such as amyloid-β, tau protein, and amyloid precursor protein, were found to be increased in persons with morbid obesity, without cognitive disorders, in comparison with non-obese controls [107]. Increased concentration of amyloid proteins in blood plasma has also been observed in obese individuals [108].

5.3. The role of low-grade systemic inflammation and neuroinflammation

The key concept linking obesity to cognitive dysfunction relates to obesity-induced low-grade systemic inflammation, which is also associated with local inflammation in the brain [109]. It is well established that hypertrophied white adipocytes, as well as mononuclear leukocytes (monocytes and lymphocytes) infiltrating fat tissue in obesity, produce a number of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).

IL-1β and IL-6 can impair the functioning of neuronal circuits responsible for cognitive performance [110]. A meta-analysis by Koyama et al. [111] (n = 5717) has shown that elevated plasma levels of C-reactive protein and IL-6 were associated with increased risk of all-cause dementia. When elevated above certain levels, proinflammatory cytokines in the blood can influence the brain, inducing neuroinflammation [112]. Obesity in db/db mice, due to genetic deletion of the leptin receptor gene, was found to be linked to increased expression of TNF-α, IL-1β, and IL-6 in the hippocampus [113].

Recently, much emphasis has been placed on the process of neuroinflammation in the hypothalamus that develops in obesity due to the central effects of elevated proinflammatory cytokines and free fatty acids. It has been suggested that circulating cytokines can reach the hypothalamus through cerebral areas of increased BBB permeability, such as the arcuate nucleus, subfornical organ, and area postrema, collectively called the circumventricular organ. There are also data indicating that obesity may be associated with an increase in BBB permeability in the cerebral areas normally endowed with a functionally competent BBB. Increased BBB permeability was observed in a prospective study of persons having obesity or excessive body weight in middle age, almost 25 years after enrollment [114]. Feeding rats with a high-fat and high-cholesterol diet for 6 months resulted in increased BBB permeability and microgliosis in the hippocampus [115]. These findings have led to the suggestion that the BBB of the hippocampal area might exhibit a much lower threshold for permeability increase than other brain areas in the context of obesity.

Proinflammatory cytokines cause microglial stimulation and proliferation in the hypothalamus, which is accompanied by activation of nuclear transcriptional factor κB (NFκB), a key transcriptional regulator of genes involved in inflammation [116]. The consequences of increased expression of proinflammatory cytokines in the hippocampus, hypothalamus, and, presumably, other cerebral areas include intensification of amyloid-β production, reduction of neurogenesis, initiation of oxidative stress, and endoplasmic reticulum stress [117]. Taken together, these factors may be implicated in the development of cognitive dysfunction in obesity. Local inflammation in the hypothalamus is associated with the formation of leptin- and insulin-resistance, which establishes a vicious cycle of progressively increasing food consumption and body weight gain.

5.4. Obesity and adipokine imbalance

Obesity is characterized by elevated plasma levels of leptin and reduced levels of anti-inflammatory adipokines, such as adiponectin [118]. Under normal conditions, leptin positively regulates a number of physiological processes critical for cognitive function, such as long-term potentiation [119], synaptic transmission, and plasticity [120], and prevention of amyloid-β accumulation and tau hyperphosphorylation [121]. Hyperleptinemia in obesity cannot overcome central leptin resistance, which may result in alteration of the above processes and thereby contribute to the pathogenesis of cognitive dysfunction in obesity.

Another adipokine that is protective in terms of cognitive function, is adiponectin. Adiponectin can contribute to normalization of central insulin resistance by virtue of increased neuronal sensitivity to insulin [122]. In addition, it modulates synaptic plasticity and augments synaptogenesis [123], decreases production and aggregation of amyloid-β [124], and exerts neuroprotective effects in rodent models of ischemic and hemorrhagic stroke [125]. Thus, adipokine imbalance is currently viewed as an important mechanism involved in cognitive dysfunction in obesity, while normalization of altered leptin and adiponectin signaling in the brain is emerging as one of the valid targets for prevention and treatment of dementia.

6. Concluding remarks

Published epidemiological studies and systematic reviews suggest that MS increases the risk for VD and progression from mild cognitive impairment to overt dementia. However, the evidence for whether MS increases incident dementia and AD, as well as precipitates cognitive decline in older persons, is largely circumstantial. Large-scale, adequately powered clinical trials with repeated measurement in a longer follow-up period are necessary to understand whether MS has a significant impact on AD and cognitive decline in the older population.

The pathogenesis of dementia in MS is multifactorial, with the involvement of both vascular injury and non-ischemic neuronal death due to neurodegeneration. Classically, VD and AD are considered two different diseases with a clear boundary separating one type of dementia from another. However, accumulating evidence indicates that the overlap between cerebrovascular disorders and neurodegeneration may actually be underestimated, as evidenced mainly by the observations that many patients have coexisting vascular lesions and pathological protein deposition. VD and AD have similar risk factors, which in fact represent classical MS components, such as obesity, AH, DM, and atherogenic dyslipidemia. Next, it should be emphasized that neurodegenerative and ischemic lesions do not simply coexist in the brain due to parallel, independent evolution, but rather exacerbate each other, leading to more severe consequences for cognition than would either pathology alone. On one hand, cerebral ischemia increases amyloid-β generation and impairs its clearance [126]. Ischemia contributes to activation of β-/γ-secretase, the enzymes responsible for proteolytic cleavage of amyloid precursor protein, leading to amyloid-β production [127,128]. Additionally, cerebral ischemia is associated with tau hyperphosphorylation [129]. On the other hand, neurodegeneration can also potentiate the harmful effects of ischemia. For example, amyloid peptides exert a vasoconstrictive effect on cerebral vessels [130] and are able to accumulate in the vessel wall matrix, causing it to thicken and leading to loss of vascular smooth muscle cells [131].

Despite significant progress in our understanding of the mechanisms of cognitive dysfunction in MS over the last few decades, it is evident that many critical questions remain unanswered. Additional studies will be required to define which specific cognitive domains are most sensitive to the constellation of injurious factors inherent to MS. It is also critical to quantitate the contribution of classical MS components to cognitive function, in comparison to that of other risk factors that are not related to MS. The most important question relates to the potentiating effects of isolated MS components on the progression of cognitive dysfunction. It is crucial to determine whether the net cognitive dysfunction in MS simply represents the sum of the negative impact of obesity, AH, and DM, or whether the combination of several factors in full MS exerts a synergistic effect, multiplying the injury of cognitive function-related brain areas. Few reports on this topic have become available in the literature in recent years. For instance, Fan et al. [132] demonstrated that the development of hypertension, hyperlipidemia, or both, following a diagnosis of incident DM, was not associated with an additional increase in the risk of dementia, which points to the predominant role of DM in the pathogenesis of cognitive impairment. Although, in general, the severity of MS is negatively correlated with cognitive function, obesity as an isolated component of MS was shown to exert a paradoxical protective effect against cognitive dysfunction in the same cohort of patients [133].

The evidence summarized in the review indicates that, in addition to universal mechanisms underlying cognitive dysfunction shared by all MS components, there are additional pathogenetic pathways leading to cognitive deficits and dementia that are specific for each component. The examples of such component-specific pathogenetic pathways include central insulin-resistance and hypoglycemia in DM, neuroinflammation and adipokine imbalance in obesity, as well as arteriolosclerosis and lipohyalinosis in AH. A more detailed understanding of

cognitive disorders based on the recognition of underlying molecular mechanisms will facilitate the development of new methods for prevention and treatment of devastating cognitive decline in MS in future.

Declaration of competing interest

The authors have declared that no competing interests exist.

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