Sedentary Lifestyle and Masticatory Dysfunction

Subjects: Anatomy & Morphology

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Unhealthy brain aging and cognitive decline associate with a sedentary lifestyle and, at a cellular level, this is accompanied by astrocyte hypertrophy, myelin dysregulation, neurovascular dysfunction and the impairment of neurogenesis.

Keywords: mastication ; environment ; aging ; cognitive decline ; astrocyte morphometry ; dentate gyrus

1. Introduction

Unhealthy brain aging and cognitive decline associate with a sedentary lifestyle and, at a cellular level, this is accompanied by astrocyte hypertrophy, myelin dysregulation, neurovascular dysfunction [1] and the impairment of neurogenesis [2]. Highly sedentary humans (≥8 h/day) display reduced hippocampal volumes and increased white matter (WM) hyperintensities [3][4] that are associated with accelerated cognitive, neuropsychiatric and functional decline [5]. In addition to the changes associated with a sedentary life, it has become clear that oral dysfunction is present in the same individuals and that this group feature is also associated with dementia or mild cognitive decline [6][7][8][9][10][11][12][13]. While it is not clear whether poor oral health predicts dementia, substantial data suggests that oral health declines as cognitive impairment and dementia progresses [7][12][14][15][16]. Furthermore, it has been demonstrated that masticatory exercise improves cognitive function in older adults [17] and thus the link between cognitive decline and masticatory dysfunction is now clear [8][18][19][20][21][22]. As loss of masticatory activity [8][11][12][13][18][19][20][21][22] and sedentary life style [23][24] are risk factors for age-related cognitive decline, there is a need to focus attention on those sub-populations that experience greater oral health deterioration or impairment of the stomatognathic system, and those having living sedentary lives.

Several experimental models of masticatory dysfunction have been explored to clarify the cellular and molecular mechanisms associated with memory impairment [25][26][27]. From these studies, it can be learned that chewing maintains hippocampus-dependent cognitive function [18], and that age-related spatial memory deficits can be aggravated by a sedentary lifestyle and a reduction in masticatory activity [26][28][29][30][31]. In agreement with the findings described above, oral rehabilitation and environmental enrichment act in concert to restore spatial memory decline in aged mice [31]. In rat models of occlusal disharmony, amyloid-β is increased in the hippocampus and this was also associated with cognitive dysfunction [32][33]. Studies in similar mouse models of occlusal disharmony report significant increases in the expression of interleukin-1β in the brain, which was later accompanied by the appearance of amyloid-β and hyperphosphorylated tau in the hippocampus, and the induction of learning and memory deficits [34].

At the cellular level, cognitive decline has been linked to neuroinflammation via the enhanced activation of astrocytes, oligodendrocytes, and microglia [35][36][37] and these events are underscored by the presence of specific molecular signatures in the aging brain [38][39][40].

As a function of environmental stimuli [41][42], age [43][44], or the presence of other pathology [45][46][47], astrocytes differentially respond to changes in the microenvironment of the brain, in both form and function [48][49]. For example, physical exercise induces astrocyte proliferation and morphological changes, which alters the interplay between astrocytes, microglia and neurons to enhance neuroplasticity [23][50][51][52]. A distinctive pattern of gene expression is also induced in regions of the brain that are activated by exercise [53]. An enriched environment also induces neuroplastic changes in the dorsoventral hippocampal regions [54][55], increasing BDNF levels, p-AKT and p-MAPK1/2 and preventing neuroplastic decline by increasing the formation of dendritic spines and new neurons [24].

In rodent models of dysfunctional mastication, induced either by tooth loss, raised bite or soft diet, cognitive decline is associated with differential effects on astrocytes in different areas and different layers within the same greater brain region [56][57][58][59]. Indeed, five transcriptionally distinct astrocyte subtypes have been found in the mouse hippocampus [60][61].

In aged brains, previous transcriptomic analysis has revealed that there is upregulation of reactive astrocyte genes [62], which includes the expression of genes for neuroinflammation, synapse elimination pathways, and decreased cholesterol synthesis enzymes [63]. These changes were accompanied by an increase of A1 reactive astrocytes, which are argued to release a neurotoxic factor that induces neuronal death and cognitive decline [62]. In addition, dysregulated astrocytes and astrogliosis with an increased expression of GFAP and cellular hypertrophy [64] have been shown to be associated with impaired memory function in late life [65].

From optogenetics and chemogenetics studies, in which astrocytes can be selectively manipulated, emergent data has provided evidence that astrocytes directly participate in cognition [66][67][68][69], and other behavioral functions, including sensorimotor behaviours [70][71], sleep [72], feeding [73], fear and anxiety [74][75], and this is associated with regulation of synapses and circuits (see [76][77] for recent reviews).

2. Running, Experiencing Novelty, and Mastication to Learn Faster, Better Remember, and Enhance Individual Ethological Behavior

It is well known that long-term voluntary running improves learning and memory, by enchancing the strength of neuronal connections, through synaptic plasticity in the hippocampus [78][79], and increasing neurogenesis [55][80]. Continuous voluntary wheel running exercise also contributes to astrogenesis and the repopulation of microglia [81]. The voluntary running-enhanced plasticity seems to be mediated by the Notch1 signaling pathway [82] and brain-specific angiogenesis inhibitor 1 (BAI1) [83]. In the absence of exercise, short-term [84] and lifelong environmental enrichment are able to improve memory and postpone age-related cognitive decline [85]; but for rodents enriched cages usually combine elements for physical exercise and cognitive stimuli. Indeed, running wheel, toys, tunnels, bridges, ropes, stairs, which are replaced or displaced from time to time (1 or 2 weeks) [86][87], encourage locomotor and exploratory activity in these cages, whereas the absence of these elements in standard laboratory cages do not.

The elements inside enriched cages provide novelty, visuo-spatial and somatomotor stimuli and social interaction, but the stimuli for neurogenesis and the release of neurotrophins originate from voluntary exercise [88]. Comparative effects of the elements provided by an enriched environment have enabled the disentanglement of the influence of novelty, social and physical activity and behavioral performance in hippocampal-dependent tasks. Indeed, well designed comparative studies demonstrated that running stimulates hippocampal neurogenesis, while a complex environment does not. A complex environment, and not running, increases depolarization-associated c-fos expression and reduces plasma corticosterone [89]. However, the combination of cognitive stimuli, social interaction, and physical exercise was found to be the most effective way to reduce neuropathological outcomes in a transgenic mouse model of cerebral amyloid angiopathy [90].

Innate behavioral and physiological programs ensure survival and must be flexible enough to cope with environmental changes and build adaptive responses [91][92]. The impoverished environment of standard laboratory housing is associated with reduced display of species typical behaviors, whereas enriched cages seem to enhance ethological natural behaviors and increase individualized behavior in mice [55][93]. Hiding behavior is a good example of the innate repertoire to avoid attack and predation and this is a species-specific response that may explain the tendency of a mouse to avoid open/lit areas and to spontaneously explore unfamiliar areas [94]. In an open arena, for example, this mouse behavior is readily recognized as a preference for the safety of the peripheral zone of the open field [95]. Another innate typical behavior is related to the detection and exploration of novelty. In general terms, novelty is defined as a new event with which partial or no previous experience has occurred [96], being classified respectively as contextual/spatial novelty or stimulus novelty [97]. Enriched cages provide periodic inanimate object novelty and complexity through alterations in the physical and social environment, and these elements enhance sensory, cognitive and physical stimulation [98]. Similarly, an enriched environment enhances spatial learning, reversal learning and memory through the balance of excitatory and inhibitory synaptic densities [99]. The exploration of novelty related to a social stimulus or object recognition in rodents is known to activate different neural circuits [96], which appear to be an evolutionary adaptive response to provide parallel processing for novelty.

Oral and cognitive health are interconnected [100] and the recovery of masticatory activity can prevent cognitive decline [101][102][103]. The use of dental human prostheses successfully reduces cognitive consequences of masticatory dysfunction [104]. In animal studies, the relation between decrease in masticatory activity, due to a soft diet [28][30][105] or tooth loss [106], and memory impairment have been previously demonstrated [107]. Similarly, occlusal disharmony induces spatial memory impairment [29][106][108][109][110] and chronic stress [111][112][113]. Coherently, mastication activity, as a stress-coping behavior [114], is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis and hippocampus [115].

Mice housed in standard cages have reduced physical fitness and impaired thermoregulation, which leads to decreased ethological behavior and welfare [116]. In addition, long-term powdered diet increases the spontaneous locomotor activity of mice and their social interaction or impulsive and anxiety-like behaviors in elevated-plus-maze tasks [117]. These changes are associated with significant modifications in dopaminergic/noradrenergic systems and γ-aminobutyric acid-ergic (GABAergic) mediations in the frontal cortex [118]. In contrast, chewing prevents stress-induced hippocampal long-term depression (LTD) formation and anxiety-related behaviors, while ameliorating stress-induced suppression of hippocampal long-term potentiation (LTP) [119] via histamine H1 receptor [119]. Indeed, gene expression after weaning varies as a function of soft (reduced masticatory activity) or chow (normal masticatory activity) diets. Here, gene ontology analysis of differential expression in the thalamus showed that glutamate decarboxylase, GABA receptors and the vesicular GABA transporter were upregulated in the chow diet group, whereas dendritic spine morphogenesis was downregulated, with a significant reduction in the number of spines at the ventral posterolateral and posteromedial nucleus [120].

The hypothalamic paraventricular nucleus (PVN), a high order integration center between the neuroendocrine and autonomic nervous systems, is affected by chewing, which reduces the number of corticotropin releasing factor positive cells inhibiting the autonomic releasing of adrenaline and noradrenaline via locus coeruleus [120].

3. Enriched Environment and Masticatory Rehabilitation to Prevent Synaptic Dysfunction Associated with Age-Related Cognitive Decline

In animal models all the approaches that have been used to induce masticatory dysfunction (soft diet feeding, molar extraction and bite raising) are associated with impairment of spatial learning and memory, a reduction of the number of hippocampal pyramidal neurons, the downregulation of brain derived neurotrophic factor, decreased synaptic activity, impaired neurogenesis in dentate gyrus and increased glial cell proliferation, which seem to be dose-dependent through the reduction of chewing-related stimuli (see [27][121] for systematic reviews).

The synaptic changes in form, function, and plasticity associated with learning and memory formation are interrelated in the hippocampus [122][123][124]. As the hippocampal circuits mature, the establishment of synaptic reinforcement occurs in association with lasting structural changes and long-term potentiation (LTP). The intense synaptogenesis in the developmental period is replaced by an increase and clustering of mature synapses [125] and these synaptic rearrangements are selective and strengthen the circuits related to the task being learned [126].

Functional magnetic resonance imaging studies have shown that when a comparison of the activity in the hippocampal subfields is made, the dentate gyrus (DG) is more active than the horn of Amon (CA1-CA2-CA3) and the subiculum, and that in both the coding process and information retrieval, the rostral (septal) pole is more active than the caudal (temporal) pole [127]. In fact, adult rats trained to remember the spatial location of an object, exhibited remodeling of synapses 6 h later in the molecular layer of the dorsal DG (septal) (DG-Mol) [128].

The entorhinal-to-dentate gyrus pathway is involved in memory formation carrying spatial and non-spatial information through the medial and lateral perforant excitatory pathways onto granule cells [129][130]. Astrocytes sense local synaptic transmission in the molecular layer of the dentate gyrus and control these inputs to the dentate granule cells at the presynaptic level [131][132][133].

Evidence has now emerged in rodents that the astrocyte is an essential mediator of learning and memory [133] and that astrocytic ephrin-B1 controls synapse formation in the hippocampus during learning and memory by regulating new dendritic spine formation and clustering on hippocampal neurons activated during memory recall [134]. Astrocytic processes encapsulate synapses allowing bidirectional communication with neurons [134] through G-protein-coupled receptors influencing learning and memory [135]. The activation of hippocampal astrocytes enhances synaptic potentiation and memory acquisition [66][136][137].

4. Dentate Gyrus Astrocytes, Long Life Sedentary Lifestyle and Dysfunctional Mastication

It is known that physical exercise promotes morphological changes in astrocytes, and astrocytes may contribute to episodic memory function [42][138]. Astrocytic activation is necessary for synaptic plasticity and is sufficient to induce NMDA-dependent long-term potentiation in the hippocampus in a task-specific way, coupled with learning [136].

In general, astrocyte arbors with the greater complexity phenotype (AST1) from an enriched environment, independent of masticatory regimen or age, showed thinner and more ramified branches than astrocytes from mice raised in an

impoverished environment. This effect, however, is not readily recognized in astrocytes with the lower complexity phenotype (AST2). Thus, AST1 and AST2 morphological complexities are diversely affected by environment, aging and masticatory dysfunction, suggesting that astrocyte morphology does not respond linearly to these influences and that these morphotypes may have differential physiological roles.

Astro-glial morphological atrophy and loss of function seem to be part of neuropathological changes of the aging brain [139], and astrosenescence is characterized by loss of function and neuroinflammation, which seem to be central components to the mechanisms of age-related neurodegenerative disorders [35]. Astrocyte senescence is associated with an increased expression of glial fibrillary acid protein and vimentin [140], and aged astrocytes are associated with the releasing of chemokines, cytokines, and proteases [63][141]. Morphological [86] and metabolic astrocyte changes [142] also emerge as aging progresses and these changes can be aggravated by a sedentary lifestyle and masticatory dysregulation [30][31][143][144][145].

It has been suggested that astrocytes exhibit two main phenotypes associated with a proliferative profile surrounding areas of damaged tissues and a non-proliferative, but reactive, profile retaining basic structural organization and cell interactions in intact tissues [146]. All reconstructed astrocytes previously described [59] retained basic structural organization in intact tissue, suggesting that AST1 and AST2 phenotypes are indeed subtypes of a non-proliferative, reactive profile.

5. Differential Effects of Sedentary Lifestyle and Masticatory Dysfunction on Dorsal/Ventral Dentate Gyrus Morphological Phenotypes

Although dorsal and ventral hippocampal regions show similar laminar and cellular organization, their connectivity to other brain regions are different [147][148][149][150][151]. They exhibit differential rates of neurogenesis and each displays a distinct pattern of neurotransmitter receptor distribution [152][153][154]. In addition, the septal/temporal divisions of the hippocampus exhibit significant differences in behavior-induced arc gene expression [155], distinct transcriptional and epigenetic effects in response to an enriched environment or physical activity [82][156], and distinct pathological responses throughout aging [157]. The dorsal hippocampus is associated with spatial memory and contextual information processing, while the ventral hippocampus is related to emotional behavior in association with fear, anxiety, and reward processing [158][159][160]. For example, small lesions in either the dorsal or ventral hippocampus generate distinct behavioral impairments in working memory and reference memory retrieval [161] and normal or abnormal neurogenesis along the septal/temporal hippocampal regions, which may be connected to mental health, neurological diseases [162][163] or affective disorders [164].

A previous report, limited to search for age influence on morphological complexity of GFAP astrocytes, demonstrated remarkable heterogeneity in the age-related changes in distinct subfields and along the dorsoventral axis of the hippocampus and in the entorhinal cortex of C57Bl6 mice [157]. These authors found that compared to 6-month-old mice the number of intersections, as a function of soma distance, increased significantly in dorsal dentate gyrus of 14-month-old mice, and the total sum of intersections, the number of processes and the total branch length followed a similar tendency, but no changes were observed in the ventral dentate gyrus.

Recently [165], cyclic multiplex fluorescent immunohistochemistry was used to classify astrocytes morphologically in normal aging and Alzheimer's Disease, and showed three main phenotypes of astrocytes: homeostatic, intermediate, and reactive. Reactive astrocytes and, to a lesser extent, intermediate astrocytes were associated with Alzheimer's disease pathology. The intermediate astrocytes were suggested to represent a transitional state between reactive and homeostatic or to represent a resilience mechanism. These authors concluded that the classic binary "homeostatic vs. reactive" classification for astrocytes, but also relevant to microglia, may now include a third state that may represent gain or loss of function. Nevertheless, recent literature points out that astrocytes are heterogeneous and dynamic phenotypes with timing- and context-dependent states [74][146][166].

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