Review Article

Stress and the glymphatic system

Mariya Ivanovska[1, 2], Meral Naimova [3], Marianna Murdjeva [1, 2]

[1] Department of Microbiology and Immunology, Faculty of Pharmacy; Research Institute, Medical University-Plovdiv, Bulgaria
[2] Laboratory of Clinical Immunology, University Hospital "St. George"- Plovdiv, Bulgaria
[3] Student in medicine 5th year, Medical University-Plovdiv, Bulgaria

For correspondence:

Mariya Ivanovska, M.D, Ph.D
Department of Microbiology and Immunology; 15A, Vassil Aprilov Blvd. 4002 Plovdiv, MU-Plovdiv, Bulgaria
E-mail: mariya.ivanovska@mu-plovdiv.bg; ORCID:0000-0001-9028-2192

Keywords: glymphatic system, stress, PNEI, immune system

List of abbreviations:

PNEI - psychoneuroendocrinoimmunology
CNS - Central nervous system
CSF - Cerebrospinal Fluid
AQP4 - Aquaporin-4
HPA - hypothalamic-pituitary-adrenal
AD - Alzheimer's disease
PD - Parkinson's disease
Aβ - Amyloid beta
TBI - Traumatic brain injury
NE - norepinephrine
SAH - Subarachnoid hemorrhage
REM – rapid eye movement

1. Summary

Background: Psychoneuroendocrinoimmunology (PNEI) is an integrative discipline studying the processes by which mental events modulate immune functions and how the immune system in turn can alter brain function. The central nervous system (CNS) is the only system in the body lacking its own anatomically defined lymphatic vessels. The glymphatic system is an adaptation mechanism developed by the CNS for fluid balance and waste clearance. Prolonged exposure to stress – chronic stress, can be detrimental for the functioning of the central nervous system and the glymphatic system.

Methods: Electronic databases including PubMed/MEDLINE, Google Scholar, and Scopus were searched for original articles examining stress and its effects on the glymphatic system.

Results: Numerous everyday situations can be defined as “stressful” – work environment, exams, physical and psychological stress due to illness, trauma, etc. The body’s response to stress is a combination of adjustments known as “fight-flight-freeze” response – hormonal and physiologic changes helping the body fight a threat or flee to safety. Increase in stress is associated with impaired sleep and considering that the brain’s waste clearing system is shown to be active during sleep, it can be suggested that this is a mechanism in which stress affects glymphatic function.

Conclusion: The research on the impact of stress on the glymphatic function is still lacking, but there are clear indications that researching the topic is valuable. It is

promising to evaluate if through stress management there can be an improvement in waste-clearing in the brain and the prognosis of diseases characterized by accumulation of metabolites.

2. Introduction

The central nervous system is the only system in the body that does not have its own anatomically defined lymphatic vessels [1] but has developed one of a kind adaptation mechanism to keep fluid balance and remove interstitial waste. In 2013, Nedergaard [2] discovered the glymphatic system, which is a waste clearance system, consisting of astroglia cells that form perivascular tunnels, promoting the elimination of soluble proteins, metabolic waste products and the distribution of glucose, lipids, neuromodulators, amino acids and growth factors in the brain [2]. Since the discovery of this pathway, significant research has been done to further analyze its physiological function and also explore its role in several diseases [3].

What this article will focus on is the role of stress on the brain. In a medical or biological context stress is a physical, mental, or emotional factor that causes bodily or mental tension. The brain is the main organ that plays a role in the physiological and behavioral responses to stressful agents and weather their effect is promoting or damaging to overall health. Changes in the brain when exposed to stressors lead to changes in metabolic, cardiovascular and immune systems of the body and determine the short- and long-term effects of stress [4]. The intimate mechanisms of changes in the glymphatic system when exposed to chronic stress are to be of interest because of the vital role of the brain waste clearance pathway in the riddance

of substances that accumulate and lead to neurodegenerative diseases including Alzheimer's disease, which is characterized by the accumulation of proteins, including amyloid plaques and tau tangles [5,6,7].

3. Aims of the review

This paper aims to understand better the connection between the glymphatic system and stress.

4. Methods

We have searched online libraries, including PubMed/MEDLINE, Google Scholar, and Scopus. The main search terms were “Glymphatic System” [MeSH] or “glymphatic system” [MeSH] and “stress” [MeSH]” and “sleep”, and “brain” [MeSH] with filters activated, namely publication date from 01/01/1990 to 31/12/2019 and papers written in English.

5. Discussion

5.1. Glymphatic pathway-the waste cleaning system in CNS

Cerebrospinal fluid (CSF) and the interstitial fluid in the brain are in constant communication. The facilitation of this connection is by convective influx of cerebrospinal fluid through the periarterial space [8]. From the subarachnoid space CSF follows the low resistance pathway until it reaches the dense brain parenchyma, where it is transported by Aquaporin-4 (AQP4) water channels that are in the astrocytic end feet around the brain vessels [8]. With the passage of CSF through the parenchyma, interstitial fluid fluxes toward the perivenous spaces around the

large deep veins and drains out of the brain, reaching cervical lymphatic vessels [9]. This system that drives interchange of cerebrospinal fluid and interstitial fluid in the brain is the glymphatic system [2]. Originally in 2012, Illif et al. with the use of two-photon imaging of small fluorescent tracers demonstrate that interchange and characterize the dynamics of the glymphatic system [8]. Further research conducted with fluorescent-tagged amyloid β, pathogenic peptide in Alzheimer's disease, which was transported along this route, suggests that the glymphatic pathway is a waste clearing system in the CNS [8]. Later these characteristics were well established by several articles [10,11]. In addition to amyloid β, other suggested metabolites and solutes, cleared by the system are lactate [12] and tau proteins [13]. As well as functioning as an interstitial waste clearance system, the glymphatic system in involved in transport of nutrients [14], apolipoprotein E, signaling molecules, small lipid molecules [15,16]. Other literature suggests the involvement of the glymphatic system in the brain circulation of neuromodulators, growth factors, carrier proteins and other nutrients [17].

Having in mind the numerous ways in which the glymphatic system effects deposition and distribution of solutes and metabolites in the CNS, it can be suggested the proper function of this pathway is key for normal functioning of the brain. As a particular interest of this review article is the effect of stress on the glymphatic system. There is a number of studies looking into the effects of traumatic brain injury [18], aging [19] and other diseases in relation to the glymphatic system. However, the link between chronic stress and the glymphatic function and the

mechanism of this interaction have not fully been unraveled. Significant contribution to the matter has been the study of Wei et al. which concluded that chronic stress could impair the AQP4-mediated glymphatic transport in the brain through glucocorticoid signaling [20].

5.2. The effect of glucocorticoids on the brain physiology

Glucocorticoids, mainly the so called “stress hormone” cortisol, are secreted as a result of the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis in response to stressors [21]. While when the body reacts to an acute stressor, acting for a short period of time, the secretion of cortisol is effective in restoring the homeostasis of the body, the prolonged exposure to stress – chronic stress, can be detrimental for the proper functioning of the central nervous system [22]. Numerous publications have studied the effect of glucocorticoids on the brain physiology. McEwan has stated that glucocorticoids alter neuronal architecture by causing dendritic retraction or expansion and decreased or increased synapse density [23]. GCs are reported to inhibit local cerebral glucose utilization in the brain [24] and inhibit glucose transport in neurons, glia, and endothelial cells in vitro [25, 26]. Prolonged exposure to stress has also been reported to lead to hippocampal atrophy, cause neuron loss [27], as well as disrupt memory [28] and suppress appetite [29]. As stated above the effect of chronic stress and stress hormones on the glymphatic system has not been evaluated extensively, but Wei et al.’s research clearly indicates that it is through glucocorticoid signaling that the AQP4-mediated glymphatic transport could be impaired [20].

Other conclusions about the link between stress and impaired glymphatic function can be derived by the evidence showing that there is an association between stress and alcohol addiction [30] and there is also evidence that chronic 1.5 g/kg ethanol intake induces reactive gliosis and perturbs glymphatic function [31]. The brain's waste clearing system is shown to be active during sleep [32], and having in mind that increase in stress is associated with impaired sleep [33, 34], it can be suggested that this is an another mechanism in which stress affects the glymphatic system. But there is still need for more extensive research and in depth look at this association.

5.3. **Functioning of the glymphatic system under the effects of stress**

In the modern setting we live in, one is exposed to various situations that disturb the counterbalance of the organism as a whole and its environment. In the everyday life of a modern human, there are many situations that can be defined as "stressful" – work environment, exams, physical and psychological stress due to illness, trauma and other medical conditions. The body's response to stress is a combination of adjustments known as "fight-flight-freeze" response [35]. In its essence this response is an array of hormonal, physiologic changes designed to help the body fight a threat or flee to safety [36]. Years of research has also characterized the long-term effects of chronic stress on overall health [37]. Chronic stress has been shown to contribute to increase in blood pressure [38] atherosclerosis [39], obesity – directly or indirectly by reducing sleep and exercise [40] and brain alterations connected to depression [41] addiction [42], anxiety [43].

Although there has been extensive research on the impact of stress throughout different systems of the body, the effect of chronic stress on the glymphatic system particularly remains largely uncharted. As observed earlier in this paper the research of Wei et al. shows that chronic stress impairs the AQP4-mediated global glymphatic transport in the CNS, accompanied by decreased expression and polarization of AQP4, reduced transcription of AQP4, agrin, laminin, and dystroglycan [20]. The scarcity of the literature concerning the matter, prompts for a different approach to further evaluate the association of stress and the glymphatic system's functionality.

5.4. The role of sleep on the glymphatic system

Very particular characteristic of the glymphatic system's intimate working mechanism was analyzed by Xie et al. in 2013 [32]. Their findings suggested that sleep was associated with dramatically enhanced glymphatic clearance, which was suppressed in awake state [32]. By in-vivo 2-photon imaging of the brain's waste clearance system, it was seen that compared to anesthetized mice, the CSF influx was reduced by 90% during wakefulness [32]. The findings were similar when the same experiment was performed with mice, that were in a natural sleeping state [32]. Xie et al.'s observations indicate that the sleeping state is conducive to convective fluid flux and by that to the clearance of metabolites in the brain parenchyma, uncovering a major aspect of the functioning of the glymphatic system – it is turned on during sleep and it clears the waste products produced during the awake state of the brain [2]. Considering that the neuromodulator of the state of arousal is

norepinephrine [44], Jessen et al. suggest that it is also a key regulator of glymphatic activity, and it may be responsible for the suppression of the system during wakefulness [2]. Other studies have also stated that the glymphatic clearance is dependent on the activity of noradrenergic receptors, found to be major regulators of sleep and wakefulness [45]. In a different study, through MRI imaging, it was found that the position of the head during sleep also improved clearance of interstitial solute [46].

Several studies have looked into the close relation of stress and impaired sleep. Stress has been associated with shortened sleep, fragmentation and possible reduction of sleep stages 3 and 4 [47], and impaired sleep has been shown to increase levels of stress markers such as cortisol, which can lead to worsening effects of stress [47]. When this is taken into account, insufficient glymphatic function can be expected in every situation and state that is characterized with sleep impairment, arising from exposure to chronic stress.

5.5. Glymphatic system and somatic diseases

The glymphatic drainage of metabolites and solutes can be classified as important for the onset and progression for a number of diseases. There is substantial evidence that neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by intracellular and/or extracellular accumulation of misfolded proteins and selective neuronal death in a progressive manner [48, 49]. There are indications that the glymphatic system is suppressed in number of other diseases – e.g. traumatic brain injury (TBI) and

ischemic and hemorrhagic stroke, and that suppression of glymphatic function might further contribute to the pathophysiological mechanisms seen in these diseases [2].

In Alzheimer's disease (AD) the extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease [50]. Reduced glymphatic influx and clearance of Aβ were found in a mouse model of AD [51], and pretreatment of mice with Aβ was shown to lead to significant suppression of CSF influx, suggesting that Alzheimer's disease leads to impaired glymphatic clearance and accumulation of Aβ, which will worsen glymphatic function even further [51]. Moreover, Zuroff et al. argued that in late-onset AD, Aβ accumulation is due to defective clearance, rather an overproduction [52]. Age-associated decline in glymphatic influx and interstitial solute clearance, such as Aβ, is attributed to reduced penetration of arterial pulsations in the aging brain [17], thus clearance of Aβ was shown to get worse with age [51], so age-related risk factors would potentially worsen Aβ metabolism [53]. The increase of norepinephrine (NE) in CSF in the elderly [54] would hypothetically also result in reduced glymphatic activity and impaired removal of Aβ and tau-proteins [55], which would accelerate AD progression [10]. Musiek et al. [56] suggest that sleep disturbances might also precede symptom onset in AD and may drive disease pathology, as well as be a consequence of the disease, which correlates with the notion that the brain's waste clearing system is active during sleep, rather than in awake state [32, 57, 58]. The finding of a significant reduction in glymphatic transport before deposition of Aß in the APP/PS1 mouse model of AD [51], suggests that AD onset might even be postponed by early restoration of glymphatic flow.

Traumatic brain injury (TBI), which is an established risk factor for the early development of dementia, including Alzheimer's disease, is frequently characterized by neurofibrillary tangles of aggregated tau-protein [13]. Illif et al.'s research [13] indicates that after TBI, glymphatic function is reduced by as much as 60%, which persists for at least a month after the injury. Knock-out of the AQP4-water channel gene further exacerbates worsening of glymphatic function after TBI and facilitates the development of aggregates of tau-protein, leading to neurodegeneration in the post-traumatic brain [13]. The glymphatic system's damage, following TBI could be contributed to re-localization of AQP4 channels away from astrocytic end feet [18]. There are papers suggesting that changes in glymphatic function after TBI, as well as post-traumatic sleep disruption and the following damage to the clearance of neuropeptides may be involved in the pathogenesis of headaches following traumatic injuries [59]. The chronic disruption of the glymphatic system's working mechanism is looked at as a potential link between repetitive TBI and neurodegeneration [18].

Glymphatic function has also been studied in the context of subarachnoid hemorrhages (SAH) and ischemic strokes. There is evidence that suggests severe impairment of glymphatic function after SAH and in the acute phase of ischemic stroke, reducing clearance of metabolites and other waste products [60]. Chronic cerebral hypoperfusion after a stroke is shown to contribute to the development of post-stroke dementia by impaired amyloid clearance through the glymphatic system [61].

In Parkinson's disease (PD) excessive accumulation of toxic forms of α-synuclein has an essential role in the onset of the disease, due to imbalance between production and clearance in the brain [62]. Zou et al.'s research [63], demonstrates that there is an impairment in the glymphatic clearance of α-synuclein in the brain of A53T mice, suggesting that the dysfunction of the glymphatic system may be a crucial element in the onset and progression of Parkinson's disease [63]. In addition to this mechanism, there are also comments on the negative effect of deteriorated dopaminergic neurons, linked to alterations in REM sleep, circadian rhythms and clock gene dysfunction [64].

In type 2 diabetes mellitus there is an imbalance between increase in glymphatic influx without the same increase in the efflux of interstitial fluid, which leads to solute accumulation extracellularly and subsequent cognitive decline [65].

Through the years the effect of stress has been researched from its effect on the cardiovascular system [66], through its impact on the metabolism [67], immune system [68,69] and central nervous system [70]. There is substantial evidence connecting the glymphatic system to numerous diseases, that have a tremendous impact on the lives of many people around the globe. The proper function of this waste-clearing mechanism in the brain can be important in diagnosing, managing, treating and preventing these diseases. That is why it is important to study, research and evaluate the factors that interfere with the system. Although the direct impact of stress on the glymphatic system has not been extensively researched, there are

indications that drive us to believe that studying this correlation can be beneficial for the management of multiple diseases and conditions, affecting the CNS.

6. Conclusion

The research on the impact of stress on the glymphatic function may still be lacking, but there are clear indications that there is value in researching the topic. New findings regarding the mechanisms of the onset and progression of neurodegenerative diseases would sufficiently fill the gaps in our understanding of them and also open up numerous possibilities for their prevention, early diagnosis and treatment. Chronic exposure to stress – identified as a culprit in many diseases, including diabetes, obesity, depression and cardiovascular disease, undoubtedly plays a role in various CNS disorders as well. It is promising to evaluate if through stress management methods, via mechanisms that influence the glymphatic pathway, waste-clearing in the brain can be bettered, which in turn would lead to improvement in the prognosis of diseases where accumulation of metabolites is a major factor.

7. Acknowledgements:

All the contributing authors have participated in the manuscript. MI and MaMu designed the study. All authors (MI, MN and MaMu) contributed to the interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.

8. Conflict of Interest:

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

9. References

1. Trevaskis NL, Kaminskas LM, Porter CJH. *From sewer to saviour—targeting the lymphatic system to promote drug exposure and activity.* Nat. Rev. Drug Discov. 2015; 14(11):781–803

2. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. *The glymphatic system: a beginner's guide.* Neurochemical research. 2015 Dec;40(12):2583-99.

3. Bacyinski A, Xu M, Wang W, Hu J. *The paravascular pathway for brain waste clearance: current understanding, significance and controversy.* Frontiers in neuroanatomy. 2017 Nov 7;11:101.

4. McEwen BS. *Protective and damaging effects of stress mediators: central role of the brain.* Dialogues in clinical neuroscience. 2006 Dec;8(4):367.

5. Weller RO, Subash M, Preston SD, et al. *Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease.* Brain Pathol. 2008; 18:253–266.

6. Carare RO, Bernardes-Silva M, Newman TA, et al. *Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: Significance for cerebral amyloid angiopathy and neuroimmunology*. Neuropathol Appl Neurobiol. 2008; 34: 131–144.

7. Hawkes C, Härtig W, Kacza J, et al. *Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy.* Acta Neuropathol. 2011; 121: 431–443

8. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA. *A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β.* Science translational medicine. 2012 Aug 15;4(147):147ra111-.

9. Murtha LA, Yang Q, Parsons MW, et al. *Cerebrospinal fluid is drained primarily via the spinal canal and olfactory route in young and aged spontaneously hypertensive rats.* Fluids Barriers CNS. 2014; 11:12.

10. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, Frangione B*. Clearance systems in the brain—implications for Alzheimer disease.* Nature reviews neurology. 2015 Aug;11(8):457.

11. Simon MJ, Iliff JJ. *Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease.* Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2016 Mar 1;1862(3):442-51.

12. Lundgaard I, Lu ML, Yang E, Peng W, Mestre H, Hitomi E, Deane R, Nedergaard M. *Glymphatic clearance controls state-dependent changes in brain lactate concentration.* Journal of Cerebral Blood Flow & Metabolism. 2017 Jun;37(6):2112-24.

13. Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, Singh I, Deane R, Nedergaard M. *Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury.* Journal of Neuroscience. 2014 Dec 3;34(49):16180-93

14. Matsumae M, Atsumi H, Hirayama A, Hayashi N, Takizawa K, Sano F, Yokota K, Sorimachi T. *A new look at cerebrospinal fluid motion*. No Shinkei Geka. 2016; 44: 909–924.

15. Achariyar TM, Li B, Peng W, Verghese PB, Shi Y, McConnell E, Benraiss A, Kasper T, Song W, Takano T, Holtzman DM. *Glymphatic distribution of CSF-derived apoE into brain is isoform specific and suppressed during sleep deprivation.* Molecular neurodegeneration. 2016 Dec;11(1):1-20.

16. Thrane VR, Thrane AS, Plog BA, Thiyagarajan M, Iliff JJ, Deane R, Nagelhus EA, Nedergaard M. *Paravascular microcirculation facilitates rapid lipid transport and astrocyte signaling in the brain.* Scientific reports. 2013 Sep 4;3:2582.

17. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA. *Impairment of paravascular clearance pathways in the aging brain.* Annals of neurology. 2014 Dec;76(6):845-61.

18. Sullan MJ, Asken BM, Jaffee MS, DeKosky ST, Bauer RM. *Glymphatic system disruption as a mediator of brain trauma and chronic traumatic encephalopathy.* Neuroscience & Biobehavioral Reviews. 2018 Jan 1;84:316-24.

19. Benveniste H, Liu X, Koundal S, Sanggaard S, Lee H, Wardlaw J. *The glymphatic system and waste clearance with brain aging: a review.* Gerontology. 2019;65(2):106-19.

20. Wei F, Song J, Zhang C, Lin J, Xue R, Shan LD, Gong S, Zhang GX, Qin ZH, Xu GY, Wang LH. *Chronic stress impairs the aquaporin-4-mediated glymphatic transport through glucocorticoid signaling.* Psychopharmacology. 2019 Apr 1;236(4):1367-84.

21. Sapolsky RM, Romero LM, Munck AU. *How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions.* Endocrine reviews. 2000 Feb 1;21(1):55-89.

22. Bernstein R. *The Mind and Mental Health: How Stress Affects the Brain* [Internet]. 2016 [cited April 2020]. Available from: https://www.tuw.edu/health/how-stress-affects-the-brain/

23. McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, Nasca C. *Mechanisms of stress in the brain.* Nature neuroscience. 2015 Oct;18(10):1353-63.

24. Doyle P, Guillaume-Gentile C, Rohner-Jeanrenaud F, Jeanrenaud B. *Effects of corticosterone administration on local cerebral glucose utilization of rats.* Brain Res. 1994; 645:225–230

25. Horner HC, Packan DR, Sapolsky RM. *Glucocorticoids inhibit glucose transport in cultured hippocampal neurons and glia*. Neuroendocrinology. 1990; 52:57–63

26. Virgin C, Ha T, Packan D, Tombaugh G, Yang S, Horner H, Sapolsky R. *Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoid neurotoxicity.* J Neurochem. 1991; 57:1422–1428

27. Sapolsky R. *Why stress is bad for your brain.* Science. 1996; 273:749–750

28. Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. *Glucocorticoid-induced impairment in declarative memory performance in adult humans.* J Neurosci. 1994; 14:2047–2053

29. Sapolsky R., Romero L., Munck A. *How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions.* Endocrine Reviews. 2000; 21(1):55-89

30. Brady KT, Sonne SC. *The role of stress in alcohol use, alcoholism treatment, and relapse.* Alcohol Res Health. 1999;23(4):263–271.

31. Lundgaard I, Wang W, Eberhardt A, Vinitsky HS, Reeves BC, Peng S, Lou N, Hussain R, Nedergaard M. *Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glymphatic function.* Scientific reports. 2018 Feb 2;8(1):1-6.

32. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T. *Sleep drives metabolite clearance from the adult brain.* Science. 2013 Oct 18;342(6156):373-7.

33. Kalimo R, Tenkanen L, Härmä M, Poppius E, Heinsalmi P*. Job stress and sleep disorders: findings from the Helsinki Heart Study.* Stress Medicine. 2000 Mar;16(2):65-75.

34. Åkerstedt T, Kecklund G, Axelsson J*. Impaired sleep after bedtime stress and worries.* Biological psychology. 2007 Oct 1;76(3):170-3.

35. Friedman MJ. *The human stress response*. In N. C. Bernardy & M. J. Friedman (Eds.), A practical guide to PTSD treatment: Pharmacological and psychotherapeutic approaches. 2015; 9–19. American Psychological Association.

36. Jansen AS, Van Nguyen X, Karpitskiy V, Mettenleiter TC, Loewy AD. *Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response.* Science. 1995 Oct 27; 270(5236):644-6.

37. McEwen BS. *Protective and damaging effects of stress mediators.* New England journal of medicine. 1998 Jan 15; 338(3):171-9.

38. Lindquist TL, Beilin LJ, Knuiman MW. *Influence of lifestyle, coping, and job stress on blood pressure in men and women.* Hypertension. 1997 Jan; 29(1):1-7.

39. Manuck SB, Clarkson TB, Lusso FM, Taub DM, Miller EW. *Social stress and atherosclerosis in normocholesterolemic monkeys.* Science. 1983 May 13; 220(4598):733-5.

40. Dallman MF. *Stress-induced obesity and the emotional nervous system.* Trends in Endocrinology & Metabolism. 2010 Mar 1; 21(3):159-65.

41. Hammen C. *Stress and depression*. Annu. Rev. Clin. Psychol.. 2005 Apr 27; 1:293-319.

42. Goeders NE*. The impact of stress on addiction*. European Neuropsychopharmacology. 2003 Dec 1; 13(6):435-41.

43. Shin LM, Liberzon I. *The neurocircuitry of fear, stress, and anxiety disorders.* Neuropsychopharmacology. 2010 Jan; 35(1):169-91.

44. Berridge CW, Waterhouse BD. *The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes.* Brain Res Rev. 2003; 42:33–84.

45. O'Donnell J, Ding F, Nedergaard M. *Distinct functional states of astrocytes during sleep and wakefulness: Is norepinephrine the master regulator?.* Current sleep medicine reports. 2015 Mar 1;1(1):1-8.

46. Lee H, Xie L, Yu M, Kang H, Feng T, Deane R, Logan J, Nedergaard M, Benveniste H. *The effect of body posture on brain glymphatic transport.* Journal of Neuroscience. 2015 Aug 5;35(31):11034-44.

47. Åkerstedt T. *Psychosocial stress and impaired sleep*. Scandinavian journal of work, environment & health. 2006 Dec 1:493-501.

48. Fu H, Hardy J, Duff KE. *Selective vulnerability in neurodegenerative diseases.* Nature neuroscience. 2018 Oct;21(10):1350-8.

49. Ross CA, Poirier MA. *Protein aggregation and neurodegenerative disease.* Nature medicine. 2004 Jul;10(7):S10-7.

50. Hardy J, Allsop D. *Amyloid deposition as the central event in the aetiology of Alzheimer's disease.* Trends in Pharmacological Sciences. 1991; 12 (10): 383–88.

51. Peng W, Achariyar TM, Li B, Liao Y, Mestre H, et al. *Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease.* Neurobiol. Dis. 2016; 93: 215–25

52. Zuroff L, Daley D, Black KL, Koronyo-Hamaoui M. *Clearance of cerebral Aβ in Alzheimer's disease: reassessing the role of microglia and monocytes.* Cellular and Molecular Life Sciences. 2017 Jun 1;74(12):2167-201.

53. Qi XM, Ma JF. *The role of amyloid beta clearance in cerebral amyloid angiopathy: more potential therapeutic targets.* Translational Neurodegeneration. 2017 Dec 1;6(1):22.

54. Wang LY, Murphy RR, Hanscom B, Li G, Millard SP, et al. *Cerebrospinal fluid norepinephrine and cognition in subjects across the adult age span.* Neurobiol Aging. 2013; 34: 2287-2292.

55. Szot P. *Elevated Cerebrospinal Fluid Norepinephrine in the Elderly can Link Depression and A Reduced Glymphatic System as Risk Factors for Alzheimerâ s Disease.* Journal of Aging Science. 2016 Aug 26.

56. Musiek ES, Xiong DD, Holtzman DM. *Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease.* Experimental & molecular medicine. 2015 Mar;47(3):e148-.

57. Rasmussen MK, Mestre H, Nedergaard M. *The glymphatic pathway in neurological disorders.* The Lancet Neurology. 2018 Nov 1;17(11):1016-24.

58. Mendelsohn AR, Larrick JW. *Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases.* Rejuvenation Research. 2013 Dec 1;16(6):518-23.

59. Piantino J, Lim MM, Newgard CD, Iliff J. *Linking traumatic brain injury, sleep disruption and post-traumatic headache: a potential role for Glymphatic pathway dysfunction.* Current pain and headache reports. 2019 Sep 1;23(9):62.

60. Gaberel T, Gakuba C, Goulay R, De Lizarrondo SM, Hanouz JL, Emery E, Touze E, Vivien D, Gauberti M*. Impaired glymphatic perfusion after strokes revealed by contrast-enhanced MRI: a new target for fibrinolysis?.* Stroke. 2014 Oct;45(10):3092-6.

61. Back DB, Kwon KJ, Choi DH, Shin CY, Lee J, Han SH, Kim HY. *Chronic cerebral hypoperfusion induces post-stroke dementia following acute ischemic stroke in rats.* Journal of neuroinflammation. 2017 Dec 1;14(1):216.

62. Bobela W, Aebischer P, Schneider BL. *Alpha-Synuclein as a mediator in the interplay between aging and Parkinson's disease.* Biomolecules. 2015;5(4):2675–700.

63. Zou W, Pu T, Feng W, Lu M, Zheng Y, Du R, Xiao M, Hu G. *Blocking meningeal lymphatic drainage aggravates Parkinson’s disease-like pathology*

in mice overexpressing mutated α-synuclein. Translational Neurodegeneration. 2019 Dec;8(1):7.

64. Sundaram S, Hughes RL, Peterson E, Müller-Oehring EM, Bronte-Stewart HM, Poston KL, Faerman A, Bhowmick C, Schulte T. *Establishing a framework for neuropathological correlates and glymphatic system functioning in Parkinson's disease.* Neuroscience & Biobehavioral Reviews. 2019 May 24.

65. Jiang Q, Zhang L, Ding G, Davoodi-Bojd E, Li Q, et al. *Impairment of the glymphatic system after diabetes.* J. Cereb. Blood Flow Metab. 2017; 37: 1326–37.

66. Holman EA, Silver RC, Poulin M, Andersen J, Gil-Rivas V, McIntosh DN. *Terrorism, acute stress, and cardiovascular health: A 3-year national study following the September 11th attacks.* Archives of general psychiatry. 2008 Jan 1;65(1):73-80.

67. Hirotsu C, Tufik S, Andersen ML*. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions.* Sleep Science. 2015 Nov 1;8(3):143-52.

68. Vasileva LV, Saracheva KE, Ivanovska MV, Petrova AP, Marchev AS, Georgiev MI, Murdjeva MA, Getova DP. *Antidepressant-like effect of salidroside and curcumin on the immunoreactivity of rats subjected to a chronic mild stress model.* Food and Chemical Toxicology. 2018 Nov 1;121:604-11.

69. Dhabhar FS. *Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology.* Neuroimmunomodulation. 2009;16(5):300-17.

70. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith M, Suarez EC. *Central nervous system serotonin function and cardiovascular responses to stress.* Psychosomatic medicine. 2001 Mar 1;63(2):300-5.