LINKAGE TO OTHER MAJOR THEORIES

Currently, there is no disease-modifying treatments available in spite of an enormous amount of research focused primarily on the role of Aβ plaques and neurofibrillary tangles in neurodegeneration in patients [156–158]. However, the underlying cause/causes of AD pathology remain at large, highlighting the critical urgency we must devote to researching new hypotheses such as the one presented in this article. The substantial amount of AD heterogeneity has led to the proposal of numerous theories with various focal points ranging from genetic predisposition, abnormal accumulation of pathogenic properties, dysregulation of the CNS, and environmental risk factors, implying a high probability of multiple pathways being involved in the clinical presentation and progression of AD. However, prior postulations have overlooked sex differences in AD heterogeneity. We put forth a hypothesis that we believe has pinpointed the LC-NA system as the hub of etiology in female AD, and furthermore distinguishes the decline in LC-NA and the production of estrogens as the initiating drivers that spur the primary concentration of the aforementioned hypotheses. Although our theory is not fully supported by experimental research, dissecting and analyzing formerly disseminated publications provided the evidence needed for this defining contribution that will now require others in the field to embrace and utilize to stimulate ideas for future studies. Conducting experiments aimed at maintaining estrogens and LC-NA production may prove to provide the pertinent evidence needed in order to find suitable therapeutic interventions.

CONCLUSION

To our knowledge, this is the first article that has provided a deeper insight into the interrelationship between the disruption of the female LC-NA system, the decline of estrogens, and AD vulnerability, seeing that no studies have been conducted considering their involvement to date. Accounting for sex as a biological variable in the LC as our hypothesis suggests, may propel AD research forward. These future studies will lay the groundwork for identifying sex differences and understanding their impact on AD etiology and progression. Furthermore, this will allow prevention trials to target the LC and enhance our ability to delay the onset or slow the progression of AD before it causes irrevocable neurodegeneration.

BOX 1. LOCUS COERULEUS

The LC contains 40,000–60,000 neurons that have a remarkably extensive axonal diffusion throughout the brain [159, 160], with its efferents consisting of two ascending fiber systems innervating 1) the cortex and 2) cerebellar forebrain, as well as, a descending pathway in the periventricular bundle projecting to the spinal cord [161–163]. The LC receives afferent projections from brainstem structures, in addition to inputs from the prefrontal cortex. These connections allow the LC to integrate low-level autonomic stimuli with high level cognitive information and to transfer this signal throughout the brain [164, 165].

Upon activation, NA is discharged from the LC and acts on both α- and β-adrenergic receptors present in neurons and glial cells, thus facilitating signal transduction and diverse functions within the central nervous system (CNS) [166], ranging from regulation of arousal and autonomic function to influencing episodic memory, attention, and working memory [6, 167–171]. NA also acts as a neuromodulator regulating synaptic connections and neuroplasticity, while also promoting neurogenesis and survival [70, 172]. NA additionally provides neuroprotection by suppressing neuroinflammation, and in under certain conditions, defending neurons from amyloid-induced toxicity, excitotoxicity, metabolic, and oxidative stress [12, 20, 52, 148, 149]. LC neuron terminals also possess and release co-transmitters, such as neuropeptide Y and galanin, concurrently with NA [173], both of which have been proven to contribute to neuronal plasticity and neuroprotection [174–177]

ACKNOWLEDGMENTS

Alison Luckey is funded through the Trinity College Dublin Ussher Award.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-0404r2).

REFERENCES

[1] Mravec B, Lejavova K, Cubinkova V (2014) Locus (coeruleus) minoris resistentiae in pathogenesis of Alzheimer's disease. *Curr Alzheimer Res* **11**, 992-1001.

[2] Satoh A, Iijima KM (2019) Roles of tau pathology in the locus coeruleus (LC) in age-associated pathophysiology and Alzheimer's disease pathogenesis: Potential strategies to protect the LC against aging. *Brain Res* **1702**, 17-28.

[3] Braak H, Del Tredici K (2015) The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain* **138**, 2814-2833.
[4] Braak H, Thal DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *J Neuropathol Exp Neurol* **70**, 960-969.
[5] Ghosh A, Torraville SE, Mukherjee B, Walling SG, Martin GM, Harley CW, Yuan Q (2019) An experimental model of Braak's pretangle proposal for the origin of Alzheimer's disease: The role of locus coeruleus in early symptom development. *Alzheimers Res Ther* **11**, 59.
[6] Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Res Brain Res Rev* **42**, 33-84.
[7] Mabbott NA, MacPherson GG (2006) Prions and their lethal journey to the brain. *Nat Rev Microbiol* **4**, 201-211.
[8] Goedert M (2015) Neurodegeneration. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Abeta, tau, and alpha-synuclein. *Science* **349**, 1255555.
[9] Grudzien A, Shaw P, Weintraub S, Bigio E, Mash DC, Mesulam MM (2007) Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. *Neurobiol Aging* **28**, 327-335.
[10] Mohamed NV, Herrou T, Plouffe V, Piperno N, Leclerc N (2013) Spreading of tau pathology in Alzheimer's disease by cell-to-cell transmission. *Eur J Neurosci* **37**, 1939-1948.
[11] Carter CJ (2017) Genetic, transcriptome, proteomic, and epidemiological evidence for blood-brain barrier disruption and polymicrobial brain invasion as determinant factors in Alzheimer's disease. *J Alzheimers Dis Rep* **1**, 125-157.
[12] Feinstein DL, Kalinin S, Braun D (2016) Causes, consequences, and cures for neuroinflammation mediated via the locus coeruleus: Noradrenergic signaling system. *J Neurochem* **139 Suppl 2**, 154-178.
[13] Busch C, Bohl J, Ohm TG (1997) Spatial, temporal and numeric analysis of Alzheimer changes in the nucleus coeruleus. *Neurobiol Aging* **18**, 401-406.
[14] German DC, Manaye KF, White CL, 3rd, Woodward DJ, McIntire DD, Smith WK, Kalaria RN, Mann DM (1992) Disease-specific patterns of locus coeruleus cell loss. *Ann Neurol* **32**, 667-676.
[15] Tomlinson BE, Irving D, Blessed G (1981) Cell loss in the locus coeruleus in senile dementia of Alzheimer type. *J Neurol Sci* **49**, 419-428.
[16] Bondareff W, Mountjoy CQ, Roth M (1982) Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. *Neurology* **32**, 164-168.
[17] Mann DM, Yates PO, Marcyniuk B (1985) Correlation between senile plaque and neurofibrillary tangle counts in cerebral cortex and neuronal counts in cortex and subcortical structures in Alzheimer's disease. *Neurosci Lett* **56**, 51-55.
[18] Kelly SC, He B, Perez SE, Ginsberg SD, Mufson EJ, Counts SE (2017) Locus coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. *Acta Neuropathol Commun* **5**, 8.
[19] Zarow C, Lyness SA, Mortimer JA, Chui HC (2003) Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Arch Neurol* **60**, 337-341.
[20] Mather M, Harley CW (2016) The locus coeruleus: Essential for maintaining cognitive function and the aging brain. *Trends Cogn Sci* **20**, 214-226.
[21] Mielke MM (2018) Sex and gender differences in Alzheimer's disease dementia. *Psychiatr Times* **35**, 14-17.
[22] Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative (2014) Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol* **75**, 563-573.
[23] Holland D, Desikan RS, Dale AM, McEvoy LK (2013) Higher rates of decline for women and apolipoprotein E epsilon 4 carriers. *Am J Neuroradiol* **34**, 2287-2293.
[24] Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM, Alzheimer's Disease Neuroimaging Initiative (2015) Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y)* **1**, 103-110.
[25] Hua X, Hibar DP, Lee S, Toga AW, Jack CR, Jr., Weiner MW, Thompson PM, Alzheimer's Disease Neuroimaging Initiative (2010) Sex and age differences in atrophic rates: An ADNI study with $n = 1368$ MRI scans. *Neurobiol Aging* **31**, 1463-1480.
[26] (2021) 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* **17**, 327-406.
[27] Rettberg JR, Yao J, Brinton RD (2014) Estrogen: A master regulator of bioenergetic systems in the brain and body. *Front Neuroendocrinol* **35**, 8-30.
[28] Roberts H, Hickey M (2016) Managing the menopause: An update. *Maturitas* **86**, 53-58.
[29] Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ, Group SC (2012) Executive summary of the Stages of Reproductive Aging Workshop+10: Addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* **97**, 1159-1168.
[30] Wang Y, Mishra A, Brinton RD (2020) Transitions in metabolic and immune systems from pre-menopause to post-menopause: Implications for age-associated neurodegenerative diseases. *F1000Res* **9**, F1000 Faculty Rev-68.
[31] Inter LST (2019) Variations in reproductive events across life: A pooled analysis of data from 505 147 women across 10 countries. *Hum Reprod* **34**, 881-893.
[32] Rosario ER, Chang L, Head EH, Stanczyk FZ, Pike CJ (2011) Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. *Neurobiol Aging* **32**, 604-613.
[33] Mielke MM, Vemuri P, Rocca WA (2014) Clinical epidemiology of Alzheimer's disease: Assessing sex and gender differences. *Clin Epidemiol* **6**, 37-48.
[34] Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E (2015) Perimenopause as a neurological transition state. *Nat Rev Endocrinol* **11**, 393-405.
[35] McEwen BS, Alves SE (1999) Estrogen actions in the central nervous system. *Endocr Rev* **20**, 279-307.
[36] Cui J, Shen Y, Li R (2013) Estrogen synthesis and signaling pathways during aging: From periphery to brain. *Trends Mol Med* **19**, 197-209.
[37] Bangasser DA, Zhang X, Garachh V, Hanhauser E, Valentino RJ (2011) Sexual dimorphism in locus coeruleus dendritic morphology: A structural basis for sex differences in emotional arousal. *Physiol Behav* **103**, 342-351.

[38] Pinos H, Collado P, Rodriguez-Zafra M, Rodriguez C, Segovia S, Guillamon A (2001) The development of sex differences in the locus coeruleus of the rat. *Brain Res Bull* **56**, 73-78.

[39] Lubbers LS, Zafian PT, Gautreaux C, Gordon M, Alves SE, Correa L, Lorrain DS, Hickey GJ, Luine V (2010) Estrogen receptor (ER) subtype agonists alter monoamine levels in the female rat brain. *J Steroid Biochem Mol Biol* **122**, 310-317.

[40] Vathy I, Etgen AM (1988) Ovarian steroids and hypothalamic norepinephrine release: Studies using *in vivo* brain microdialysis. *Life Sci* **43**, 1493-1499.

[41] Bangasser DA, Wiersielis KR, Khantsis S (2016) Sex differences in the locus coeruleus-norepinephrine system and its regulation by stress. *Brain Res* **1641**, 177-188.

[42] Morrison JH, Brinton RD, Schmidt PJ, Gore AC (2006) Estrogen, menopause, and the aging brain: How basic neuroscience can inform hormone therapy in women. *J Neurosci* **26**, 10332-10348.

[43] Rocca WA, Grossardt BR, Shuster LT (2011) Oophorectomy, menopause, estrogen treatment, and cognitive aging: Clinical evidence for a window of opportunity. *Brain Res* **1379**, 188-198.

[44] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP (2015) Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**, 388-405.

[45] Edison P, Archer HA, Gerhard A, Hinz R, Pavese N, Turkheimer FE, Hammers A, Tai YF, Fox N, Kennedy A, Rossor M, Brooks DJ (2008) Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiol Dis* **32**, 412-419.

[46] McGeer PL, McGeer EG (2002) Local neuroinflammation and the progression of Alzheimer's disease. *J Neurovirol* **8**, 529-538.

[47] Rogers J, Lue LF, Walker DG, Yan SD, Stern D, Strohmeyer R, Kovelowski CJ (2002) Elucidating molecular mechanisms of Alzheimer's disease in microglial cultures. *Ernst Schering Res Found Workshop*, pp. 25-44.

[48] York EM, Bernier LP, MacVicar BA (2018) Microglial modulation of neuronal activity in the healthy brain. *Dev Neurobiol* **78**, 593-603.

[49] Presumey J, Bialas AR, Carroll MC (2017) Complement system in neural synapse elimination in development and disease. *Adv Immunol* **135**, 53-79.

[50] Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, Merry KM, Shi Q, Rosenthal A, Barres BA, Lemere CA, Selkoe DJ, Stevens B (2016) Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **352**, 712-716.

[51] Eikelenboom P, Bate C, Van Gool WA, Hoozemans JJ, Rozemuller JM, Veerhuis R, Williams A (2002) Neuroinflammation in Alzheimer's disease and prion disease. *Glia* **40**, 232-239.

[52] Feinstein DL, Heneka MT, Gavrilyuk V, Dello Russo C, Weinberg G, Galea E (2002) Noradrenergic regulation of inflammatory gene expression in brain. *Neurochem Int* **41**, 357-365.

[53] Heneka MT, O'Banion MK (2007) Inflammatory processes in Alzheimer's disease. *J Neuroimmunol* **184**, 69-91.

[54] Fakhoury M (2018) Microglia and astrocytes in Alzheimer's disease: Implications for therapy. *Curr Neuropharmacol* **16**, 508-518.

[55] Giorgi FS, Saccaro LF, Galgani A, Busceti CL, Biagioni F, Frati A, Fornai F (2019) The role of Locus Coeruleus in neuroinflammation occurring in Alzheimer's disease. *Brain Res Bull* **153**, 47-58.

[56] McGeer PL, Itagaki S, Tago H, McGeer EG (1987) Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci Lett* **79**, 195-200.

[57] Salminen A, Ojala J, Kauppinen A, Kaarniranta K, Suuronen T (2009) Inflammation in Alzheimer's disease: Amyloid-beta oligomers trigger innate immunity defence via pattern recognition receptors. *Prog Neurobiol* **87**, 181-194.

[58] Shao Y, Gearing M, Mirra SS (1997) Astrocyte-apolipoprotein E associations in senile plaques in Alzheimer disease and vascular lesions: A regional immunohistochemical study. *J Neuropathol Exp Neurol* **56**, 376-381.

[59] Amor S, Puentes F, Baker D, van der Valk P (2010) Inflammation in neurodegenerative diseases. *Immunology* **129**, 154-169.

[60] O'Sullivan JB, Ryan KM, Curtin NM, Harkin A, Connor TJ (2009) Noradrenaline reuptake inhibitors limit neuroinflammation in rat cortex following a systemic inflammatory challenge: Implications for depression and neurodegeneration. *Int J Neuropsychopharmacol* **12**, 687-699.

[61] Lenz KM, McCarthy MM (2015) A starring role for microglia in brain sex differences. *Neuroscientist* **21**, 306-321.

[62] Chavarria A, Cardenas G (2013) Neuronal influence behind the central nervous system regulation of the immune cells. *Front Integr Neurosci* **7**, 64.

[63] Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK, Kummer MP (2010) Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. *Proc Natl Acad Sci U S A* **107**, 6058-6063.

[64] Pfeilschifter J, Koditz R, Pfohl M, Schatz H (2002) Changes in proinflammatory cytokine activity after menopause. *Endocr Rev* **23**, 90-119.

[65] Vina J, Lloret A (2010) Why women have more Alzheimer's disease than men: Gender and mitochondrial toxicity of amyloid-beta peptide. *J Alzheimers Dis* **20**(Suppl 2), S527-533.

[66] Ross JA, McGonigle P, Van Bockstaele EJ (2015) Locus Coeruleus, norepinephrine and Abeta peptides in Alzheimer's disease. *Neurobiol Stress* **2**, 73-84.

[67] Miller VM, Duckles SP (2008) Vascular actions of estrogens: Functional implications. *Pharmacol Rev* **60**, 210-241.

[68] Uchoa MF, Moser VA, Pike CJ (2016) Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors. *Front Neuroendocrinol* **43**, 60-82.

[69] Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich

BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mrak R, Mackenzie IR, McGeer PL, O'Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T (2000) Inflammation and Alzheimer's disease. *Neurobiol Aging* **21**, 383-421.

[70] Marien MR, Colpaert FC, Rosenquist AC (2004) Noradrenergic mechanisms in neurodegenerative diseases: A theory. *Brain Res Brain Res Rev* **45**, 38-78.

[71] Kelly SC, McKay EC, Beck JS, Collier TJ, Dorrance AM, Counts SE (2019) Locus coeruleus degeneration induces forebrain vascular pathology in a transgenic rat model of Alzheimer's disease. *J Alzheimers Dis* **70**, 371-388.

[72] Chi OZ, Wang G, Chang Q, Weiss HR (1998) Effects of isoproterenol on blood-brain barrier permeability in rats. *Neurol Res* **20**, 259-264.

[73] Harik SI, McGunigal T, Jr. (1984) The protective influence of the locus ceruleus on the blood-brain barrier. *Ann Neurol* **15**, 568-574.

[74] Cohen Z, Molinatti G, Hamel E (1997) Astroglial and vascular interactions of noradrenaline terminals in the rat cerebral cortex. *J Cereb Blood Flow Metab* **17**, 894-904.

[75] Kalinin S, Feinstein DL, Xu HL, Huesa G, Pelligrino DA, Galea E (2006) Degeneration of noradrenergic fibres from the locus coeruleus causes tight-junction disorganisation in the rat brain. *Eur J Neurosci* **24**, 3393-3400.

[76] Ben-Menachem E, Johansson BB, Svensson TH (1982) Increased vulnerability of the blood-brain barrier to acute hypertension following depletion of brain noradrenaline. *J Neural Transm* **53**, 159-167.

[77] Seguela P, Watkins KC, Geffard M, Descarries L (1990) Noradrenaline axon terminals in adult rat neocortex: An immunocytochemical analysis in serial thin sections. *Neuroscience* **35**, 249-264.

[78] Dye JF, Leach L, Clark P, Firth JA (2001) Cyclic AMP and acidic fibroblast growth factor have opposing effects on tight and adherens junctions in microvascular endothelial cells *in vitro*. *Microvasc Res* **62**, 94-113.

[79] Mutafova-Yambolieva VN, Smyth L, Bobalova J (2003) Involvement of cyclic AMP-mediated pathway in neural release of noradrenaline in canine isolated mesenteric artery and vein. *Cardiovasc Res* **57**, 217-224.

[80] Mulder AH, Schoffelmeer AN, Stoof JC (1990) On the role of adenylate cyclase in presynaptic modulation of neurotransmitter release mediated by monoamine and opioid receptors in the brain. *Ann N Y Acad Sci* **604**, 237-249.

[81] Rubin LL, Staddon JM (1999) The cell biology of the blood-brain barrier. *Annu Rev Neurosci* **22**, 11-28.

[82] Carvey PM, Hendey B, Monahan AJ (2009) The blood-brain barrier in neurodegenerative disease: A rhetorical perspective. *J Neurochem* **111**, 291-314.

[83] Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ (2010) Structure and function of the blood-brain barrier. *Neurobiol Dis* **37**, 13-25.

[84] Zlokovic BV (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* **57**, 178-201.

[85] Baeten KM, Akassoglou K (2011) Extracellular matrix and matrix receptors in blood-brain barrier formation and stroke. *Dev Neurobiol* **71**, 1018-1039.

[86] Kelleher RJ, Soiza RL (2013) Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder? *Am J Cardiovasc Dis* **3**, 197-226.

[87] Kim SY, Buckwalter M, Soreq H, Vezzani A, Kaufer D (2012) Blood-brain barrier dysfunction-induced inflammatory signaling in brain pathology and epileptogenesis. *Epilepsia* **53**(Suppl 6), 37-44.

[88] Zlokovic BV (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* **12**, 723-738.

[89] de la Torre JC (2004) Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol* **3**, 184-190.

[90] Farkas E, Luiten PG (2001) Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog Neurobiol* **64**, 575-611.

[91] Kalaria RN (2000) The role of cerebral ischemia in Alzheimer's disease. *Neurobiol Aging* **21**, 321-330.

[92] Montagne A, Zhao Z, Zlokovic BV (2017) Alzheimer's disease: A matter of blood-brain barrier dysfunction? *J Exp Med* **214**, 3151-3169.

[93] Sagare AP, Bell RD, Zlokovic BV (2012) Neurovascular dysfunction and faulty amyloid beta-peptide clearance in Alzheimer disease. *Cold Spring Harb Perspect Med* **2**, a011452.

[94] Viswanathan A, Greenberg SM (2011) Cerebral amyloid angiopathy in the elderly. *Ann Neurol* **70**, 871-880.

[95] Burek M, Arias-Loza PA, Roewer N, Forster CY (2010) Claudin-5 as a novel estrogen target in vascular endothelium. *Arterioscler Thromb Vasc Biol* **30**, 298-304.

[96] Hughes EL, Cover PO, Buckingham JC, Gavins FN (2013) Role and interactions of annexin A1 and oestrogens in the manifestation of sexual dimorphisms in cerebral and systemic inflammation. *Br J Pharmacol* **169**, 539-553.

[97] Cristante E, McArthur S, Mauro C, Maggioli E, Romero IA, Wylezinska-Arridge M, Couraud PO, Lopez-Tremoleda J, Christian HC, Weksler BB, Malaspina A, Solito E (2013) Identification of an essential endogenous regulator of blood-brain barrier integrity, and its pathological and therapeutic implications. *Proc Natl Acad Sci U S A* **110**, 832-841.

[98] Solito E, Raguenes-Nicol C, de Coupade C, Bisagni-Faure A, Russo-Marie F (1998) U937 cells deprived of endogenous annexin 1 demonstrate an increased PLA2 activity. *Br J Pharmacol* **124**, 1675-1683.

[99] Bake S, Sohrabji F (2004) 17beta-estradiol differentially regulates blood-brain barrier permeability in young and aging female rats. *Endocrinology* **145**, 5471-5475.

[100] Duckles SP, Krause DN (2007) Cerebrovascular effects of oestrogen: Multiplicity of action. *Clin Exp Pharmacol Physiol* **34**, 801-808.

[101] Kalaria RN, Harik SI (1989) Increased alpha 2- and beta 2-adrenergic receptors in cerebral microvessels in Alzheimer disease. *Neurosci Lett* **106**, 233-238.

[102] Kalaria RN, Stockmeier CA, Harik SI (1989) Brain microvessels are innervated by locus ceruleus noradrenergic neurons. *Neurosci Lett* **97**, 203-208.

[103] Sudoh N, Toba K, Akishita M, Ako J, Hashimoto M, Iijima K, Kim S, Liang YQ, Ohike Y, Watanabe T, Yamazaki I, Yoshizumi M, Eto M, Ouchi Y (2001) Estrogen prevents oxidative stress-induced endothelial cell apoptosis in rats. *Circulation* **103**, 724-729.

[104] Smith MA, Perry G, Richey PL, Sayre LM, Anderson VE, Beal MF, Kowall N (1996) Oxidative damage in Alzheimer's. *Nature* **382**, 120-121.

[105] Stirone C, Duckles SP, Krause DN, Procaccio V (2005) Estrogen increases mitochondrial efficiency and reduces oxidative stress in cerebral blood vessels. *Mol Pharmacol* **68**, 959-965.

[106] Riedel BC, Thompson PM, Brinton RD (2016) Age, APOE and sex: Triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol* **160**, 134-147.

[107] Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, Holtzman DM, Betsholtz C, Armulik A, Sallstrom J, Berk BC, Zlokovic BV (2012) Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature* **485**, 512-516.

[108] Alata W, Ye Y, St-Amour I, Vandal M, Calon F (2015) Human apolipoprotein E varepsilon4 expression impairs cerebral vascularization and blood-brain barrier function in mice. *J Cereb Blood Flow Metab* **35**, 86-94.

[109] Fernandez CG, Hamby ME, McReynolds ML, Ray WJ (2019) The role of APOE4 in disrupting the homeostatic functions of astrocytes and microglia in aging and Alzheimer's disease. *Front Aging Neurosci* **11**, 14.

[110] Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nat Rev Neurol* **9**, 106-118.

[111] Brandon JA, Farmer BC, Williams HC, Johnson LA (2018) APOE and Alzheimer's disease: Neuroimaging of metabolic and cerebrovascular dysfunction. *Front Aging Neurosci* **10**, 180.

[112] Chapman S, Michaelson DM (1998) Specific neurochemical derangements of brain projecting neurons in apolipoprotein E-deficient mice. *J Neurochem* **70**, 708-714.

[113] Arendt T, Schindler C, Bruckner MK, Eschrich K, Bigl V, Zedlick D, Marcova L (1997) Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. *J Neurosci* **17**, 516-529.

[114] Kang SS, Ahn EH, Liu X, Bryson M, Miller GW, Weinshenker D, Ye K (2021) ApoE4 inhibition of VMAT2 in the locus coeruleus exacerbates Tau pathology in Alzheimer's disease. *Acta Neuropathol* **142**, 139-158.

[115] Damoiseaux JS, Seeley WW, Zhou J, Shirer WR, Coppola G, Karydas A, Rosen HJ, Miller BL, Kramer JH, Greicius MD, Alzheimer's Disease Neuroimaging Initiative (2012) Gender modulates the APOE epsilon4 effect in healthy older adults: Convergent evidence from functional brain connectivity and spinal fluid tau levels. *J Neurosci* **32**, 8254-8262.

[116] Sampedro F, Vilaplana E, de Leon MJ, Alcolea D, Pegueroles J, Montal V, Carmona-Iragui M, Sala I, Sanchez-Saudinos MB, Anton-Aguirre S, Morenas-Rodriguez E, Camacho V, Falcon C, Pavia J, Ros D, Clarimon J, Blesa R, Lleo A, Fortea J, Alzheimer's Disease Neuroimaging Initiative (2015) APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls. *Oncotarget* **6**, 26663-26674.

[117] Heise V, Filippini N, Trachtenberg AJ, Suri S, Ebmeier KP, Mackay CE (2014) Apolipoprotein E genotype, gender and age modulate connectivity of the hippocampus in healthy adults. *Neuroimage* **98**, 23-30.

[118] Cagnacci A, Venier M (2019) The controversial history of hormone replacement therapy. *Medicina (Kaunas)* **55**, 602.

[119] Gurvich C, Hoy K, Thomas N, Kulkarni J (2018) Sex differences and the influence of sex hormones on cognition through adulthood and the aging process. *Brain Sci* **8**, 163.

[120] Shumaker SA, Reboussin BA, Espeland MA, Rapp SR, McBee WL, Dailey M, Bowen D, Terrell T, Jones BN (1998) The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials* **19**, 604-621.

[121] Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH, Women's Health Initiative Memory Study (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* **291**, 2947-2958.

[122] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J, Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. *JAMA* **288**, 321-333.

[123] Shao H, Breitner JC, Whitmer RA, Wang J, Hayden K, Wengreen H, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Zandi PP, Cache County Investigators (2012) Hormone therapy and Alzheimer disease dementia: New findings from the Cache County Study. *Neurology* **79**, 1846-1852.

[124] Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, Brinton EA, Cedars MI, Lobo RA, Merriam GR, Neal-Perry G, Santoro NF, Taylor HS, Black DM, Budoff MJ, Hodis HN, Naftolin F, Harman SM, Asthana S (2015) Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized, controlled KEEPS-Cognitive and Affective Study. *PLoS Med* **12**, e1001833; discussion e1001833.

[125] Hodis HN, Mack WJ, Shoupe D, Azen SP, Stanczyk FZ, Hwang-Levine J, Budoff MJ, Henderson VW (2015) Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. *Menopause* **22**, 391-401.

[126] Maki PM (2013) Critical window hypothesis of hormone therapy and cognition: A scientific update on clinical studies. *Menopause* **20**, 695-709.

[127] Whitmer RA, Quesenberry CP, Zhou J, Yaffe K (2011) Timing of hormone therapy and dementia: The critical window theory revisited. *Ann Neurol* **69**, 163-169.

[128] Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA, Group MS (2005) Postmenopausal hormone therapy and Alzheimer's disease risk: Interaction with age. *J Neurol Neurosurg Psychiatry* **76**, 103-105.

[129] Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, Baracchi F, Girouard H, Misoch S, Giacobini E, Depypere H, Hampel H, Women's Brain P, the Alzheimer Precision Medicine Initiative (2018) Sex differences in Alzheimer disease - the gateway to precision medicine. *Nat Rev Neurol* **14**, 457-469.

[130] Li R, Singh M (2014) Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol* **35**, 385-403.

[131] Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, Mallampalli MP, Mormino EC, Scott L, Yu WH, Maki PM, Mielke MM (2018)

Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement* **14**, 1171-1183.

[132] Theofilas P, Ehrenberg AJ, Dunlop S, Di Lorenzo Alho AT, Nguy A, Leite REP, Rodriguez RD, Mejia MB, Suemoto CK, Ferretti-Rebustini REL, Polichiso L, Nascimento CF, Seeley WW, Nitrini R, Pasqualucci CA, Jacob Filho W, Rueb U, Neuhaus J, Heinsen H, Grinberg LT (2017) Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. *Alzheimers Dement* **13**, 236-246.

[133] Guillamon A, de Blas MR, Segovia S (1988) Effects of sex steroids on the development of the locus coeruleus in the rat. *Brain Res* **468**, 306-310.

[134] Rodriguez-Zafra M, De Blas MR, Perez-Laso C, Cales JM, Guillamon A, Segovia S (1993) Effects of perinatal diazepam exposure on the sexually dimorphic rat locus coeruleus. *Neurotoxicol Teratol* **15**, 139-144.

[135] Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ (2001) Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. *Physiol Behav* **73**, 273-283.

[136] Couto LB, Moroni CR, dos Reis Ferreira CM, Elias-Filho DH, Parada CA, Pela IR, Coimbra NC (2006) Descriptive and functional neuroanatomy of locus coeruleus-noradrenaline-containing neurons involvement in bradykinin-induced antinociception on principal sensory trigeminal nucleus. *J Chem Neuroanat* **32**, 28-45.

[137] Toro CA, Zhang L, Cao J, Cai D (2019) Sex differences in Alzheimer's disease: Understanding the molecular impact. *Brain Res* **1719**, 194-207.

[138] Han M, Kang F, Yang C, Zhai M, Zheng K, Wang T, Liu Z, Li J (2021) A comparative study of serotonin and norepinephrine as adjuncts to improve cutaneous antinociception of mexiletine in response to skin pinpricks in rats. *Int J Immunopathol Pharmacol* **35**, 20587384211016129.

[139] Irwin RW, Yao J, Hamilton RT, Cadenas E, Brinton RD, Nilsen J (2008) Progesterone and estrogen regulate oxidative metabolism in brain mitochondria. *Endocrinology* **149**, 3167-3175.

[140] Riphagen JM, van Egroo M, Jacobs HIL (2021) Elevated norepinephrine metabolism gauges Alzheimer's disease-related pathology and memory decline. *J Alzheimers Dis* **80**, 521-526.

[141] Stern Y, Barnes CA, Grady C, Jones RN, Raz N (2019) Brain reserve, cognitive reserve, compensation, and maintenance: Operationalization, validity, and mechanisms of cognitive resilience. *Neurobiol Aging* **83**, 124-129.

[142] Stern Y (2009) Cognitive reserve. *Neuropsychologia* **47**, 2015-2028.

[143] Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A (1988) Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* **23**, 138-144.

[144] Giedd JN, Raznahan A, Mills KL, Lenroot RK (2012) Review: Magnetic resonance imaging of male/female differences in human adolescent brain anatomy. *Biol Sex Differ* **3**, 19.

[145] Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA (2005) Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry* **62**, 685-691.

[146] Skup M, Zhu H, Wang Y, Giovanello KS, Lin J-a, Shen D, Shi F, Gao W, Lin W, Fan Y (2011) Sex differences in grey matter atrophy patterns among AD and aMCI patients: Results from ADNI. *Neuroimage* **56**, 890-906.

[147] Robertson IH (2013) A noradrenergic theory of cognitive reserve: Implications for Alzheimer's disease. *Neurobiol Aging* **34**, 298-308.

[148] Zucca FA, Segura-Aguilar J, Ferrari E, Munoz P, Paris I, Sulzer D, Sarna T, Casella L, Zecca L (2017) Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Prog Neurobiol* **155**, 96-119.

[149] Robertson SD, Plummer NW, Jensen P (2016) Uncovering diversity in the development of central noradrenergic neurons and their efferents. *Brain Res* **1641**, 234-244.

[150] Clewett DV, Lee TH, Greening S, Ponzio A, Margalit E, Mather M (2016) Neuromelanin marks the spot: Identifying a locus coeruleus biomarker of cognitive reserve in healthy aging. *Neurobiol Aging* **37**, 117-126.

[151] Liu KY, Kievit RA, Tsvetanov KA, Betts MJ, Duzel E, Rowe JB, Cam CAN, Howard R, Hammerer D (2020) Noradrenergic-dependent functions are associated with age-related locus coeruleus signal intensity differences. *Nat Commun* **11**, 1712.

[152] Barnes LL, Lamar M, Schneider JA (2019) Sex differences in mixed neuropathologies in community-dwelling older adults. *Brain Res* **1719**, 11-16.

[153] Betts MJ, Kirilina E, Otaduy MCG, Ivanov D, Acosta-Cabronero J, Callaghan MF, Lambert C, Cardenas-Blanco A, Pine K, Passamonti L, Loane C, Keuken MC, Trujillo P, Lusebrink F, Mattern H, Liu KY, Priovoulos N, Fliessbach K, Dahl MJ, Maass A, Madelung CF, Meder D, Ehrenberg AJ, Speck O, Weiskopf N, Dolan R, Inglis B, Tosun D, Morawski M, Zucca FA, Siebner HR, Mather M, Uludag K, Heinsen H, Poser BA, Howard R, Zecca L, Rowe JB, Grinberg LT, Jacobs HIL, Duzel E, Hammerer D (2019) Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. *Brain* **142**, 2558-2571.

[154] Liu M, Lu L, Liu Q, Bai Y, Dong A (2021) FDG PET/CT in disseminated intracranial and intramedullary spinal cord tuberculomas. *Clin Nucl Med* **46**, 266-269.

[155] Ycaza Herrera A, Wang J, Mather M (2019) The gist and details of sex differences in cognition and the brain: How parallels in sex differences across domains are shaped by the locus coeruleus and catecholamine systems. *Prog Neurobiol* **176**, 120-133.

[156] Chen GF, Xu TH, Yan Y, Zhou YR, Jiang Y, Melcher K, Xu HE (2017) Amyloid beta: Structure, biology and structure-based therapeutic development. *Acta Pharmacol Sin* **38**, 1205-1235.

[157] Gauthier S, Albert M, Fox N, Goedert M, Kivipelto M, Mestre-Ferrandiz J, Middleton LT (2016) Why has therapy development for dementia failed in the last two decades? *Alzheimers Dement* **12**, 60-64.

[158] Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT, National Institute on Aging, Alzheimer's Association (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. *Acta Neuropathol* **123**, 1-11.

[159] Samuels ER, Szabadi E (2008) Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the

regulation of arousal and autonomic function part I: Principles of functional organisation. *Curr Neuropharmacol* **6**, 235-253.

[160] Sharma Y, Xu T, Graf WM, Fobbs A, Sherwood CC, Hof PR, Allman JM, Manaye KF (2010) Comparative anatomy of the locus coeruleus in humans and nonhuman primates. *J Comp Neurol* **518**, 963-971.

[161] Szabadi E (2013) Functional neuroanatomy of the central noradrenergic system. *J Psychopharmacol* **27**, 659-693.

[162] Counts SE, Mufson EJ (2010) Noradrenaline activation of neurotrophic pathways protects against neuronal amyloid toxicity. *J Neurochem* **113**, 649-660.

[163] Jones BE, Friedman L (1983) Atlas of catecholamine perikarya, varicosities and pathways in the brainstem of the cat. *J Comp Neurol* **215**, 382-396.

[164] Avery MC, Krichmar JL (2017) Neuromodulatory systems and their interactions: A review of models, theories, and experiments. *Front Neural Circuits* **11**, 108.

[165] Schwarz LA, Luo L (2015) Organization of the locus coeruleus-norepinephrine system. *Curr Biol* **25**, R1051-R1056.

[166] Ferrucci M, Giorgi FS, Bartalucci A, Busceti CL, Fornai F (2013) The effects of locus coeruleus and norepinephrine in methamphetamine toxicity. *Curr Neuropharmacol* **11**, 80-94.

[167] Arnsten AF, Li BM (2005) Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. *Biol Psychiatry* **57**, 1377-1384.

[168] Cahill L, McGaugh JL (1996) Modulation of memory storage. *Curr Opin Neurobiol* **6**, 237-242.

[169] McGaugh JL, Roozendaal B (2009) Drug enhancement of memory consolidation: Historical perspective and neurobiological implications. *Psychopharmacology (Berl)* **202**, 3-14.

[170] Robbins TW, Roberts AC (2007) Differential regulation of fronto-executive function by the monoamines and acetylcholine. *Cereb Cortex* **17**(Suppl 1), i151-160.

[171] Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci* **10**, 211-223.

[172] Wagatsuma A, Okuyama T, Sun C, Smith LM, Abe K, Tonegawa S (2018) Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. *Proc Natl Acad Sci U S A* **115**, E310-E316.

[173] Holets VR, Hokfelt T, Rokaeus A, Terenius L, Goldstein M (1988) Locus coeruleus neurons in the rat containing neuropeptide Y, tyrosine hydroxylase or galanin and their efferent projections to the spinal cord, cerebral cortex and hypothalamus. *Neuroscience* **24**, 893-906.

[174] Angelucci F, Gelfo F, Fiore M, Croce N, Mathe AA, Bernardini S, Caltagirone C (2014) The effect of neuropeptide Y on cell survival and neurotrophin expression in *in-vitro* models of Alzheimer's disease. *Can J Physiol Pharmacol* **92**, 621-630.

[175] Borbely E, Scheich B, Helyes Z (2013) Neuropeptides in learning and memory. *Neuropeptides* **47**, 439-450.

[176] Counts SE, Perez SE, Ginsberg SD, Mufson EJ (2010) Neuroprotective role for galanin in Alzheimer's disease. *Exp Suppl* **102**, 143-162.

[177] Spencer B, Potkar R, Metcalf J, Thrin I, Adame A, Rockenstein E, Masliah E (2016) Systemic central nervous system (CNS)-targeted delivery of neuropeptide Y (NPY) reduces neurodegeneration and increases neural precursor cell proliferation in a mouse model of Alzheimer disease. *J Biol Chem* **291**, 1905-1920.