
Related Articles


Dement Geriatr Cogn Disord. 2020 Jan 28;:1–16


Abstract

BACKGROUND: Changes in cerebrospinal fluid, neuroimaging, and cognitive functions have been used as diagnostic biomarkers of Alzheimer’s disease (AD). This study aimed to investigate the temporal trajectories of plasma biomarkers in subjects with mild cognitive impairment (MCI) and patients with AD relative to healthy controls (HCs).

METHODS: In this longitudinal study, 82 participants (31 HCs, 33 MCI patients, and 18 AD patients) were enrolled. After 3 years, 7 HCs had transitioned to MCI and 10 subjects with MCI had converted to AD. We analyzed plasma amyloid beta (Aβ) and tau proteins at baseline and annually to correlate with biochemical data and neuropsychological scores.

RESULTS: Longitudinal data analysis showed an evolution of Aβ-related biomarkers over time within patients, whereas tau-related biomarkers differed primarily across diagnostic classifications. An initial steady increase in Aβ42 in the MCI stage was followed by a decrease just prior to clinical AD onset. Hyperphosphorylated tau protein levels correlated with cognitive decline in the MCI stage, but not in the AD stage.

CONCLUSION: Plasma Aβ and tau levels change in a dynamic, nonlinear, nonparallel manner over the AD continuum. Changes in plasma Aβ concentration are time-dependent, whereas changes in hyperphosphorylated tau protein levels paralleled the clinical progression of MCI. It remains to be clarified whether diagnostic efficiency can be improved by combining multiple plasma markers or combining plasma markers with other diagnostic biomarkers.

PMID: 31991443 [PubMed — as supplied by publisher]

Memory-enhancing effects of 7,3′,4′-trihydroxyisoflavone by regulation of cholinergic function and BDNF signaling pathway in mice.

Related Articles

Memory-enhancing effects of 7,3′,4′-trihydroxyisoflavone by regulation of cholinergic function and BDNF signaling pathway in mice.

Food Chem Toxicol. 2020 Jan 25;:111160

Authors: Kim SK, Ko YH, Lee SY, Jang CG

Abstract

7,3′,4′-Trihydroxyisoflavone (THIF) is a secondary metabolite derived from daidzein and is abundantly present in soybeans. Daidzein and 7,3′,4′-THIF exhibit several pharmacological activities, including antioxidant and anti-atopic properties. However, the effects of 7,3′,4′-THIF on cognitive function have not been fully investigated. Here, we evaluated the effects of 7,3′,4′-THIF on memory using Y-maze and passive avoidance tests. The positive control groups were given donepezil (5 mg/kg, p.o.) or piracetam (200 mg/kg, i.p.) and the treated groups were given 7,3′,4′-THIF (0.25, 0.5 and 1 mg/kg, p.o.), 7,3′,4′-THIF at 1 mg/kg and donepezil at 5 mg/kg effectively ameliorated memory impairments induced by scopolamine (0.5 mg/kg, i.p.) in mice. In addition, 7,3′,4′-THIF at 1 mg/kg and piracetam at 200 mg/kg significantly enhanced memory in normal mice. To examine the underlying mechanisms of 7,3′,4′-THIF on cognition following behavioral experiments, biochemical tests were performed in the whole hippocampus. 7,3′,4′-THIF at 1 mg/kg, p.o. significantly recovered scopolamine-induced cholinergic impairments. Moreover, brain-derived neurotrophic factor (BDNF), postsynaptic density protein-95 (PSD-95), and synaptophysin, along with phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and cAMP response element binding (CREB), were significantly increased by 7,3′,4′-THIF (1 mg/kg, p.o.). Our findings indicate that 7,3′,4′-THIF improves cognitive function by regulating cholinergic system and BDNF signaling.

PMID: 31991199 [PubMed — as supplied by publisher]
Exercise effects on brain and behavior in healthy mice, Alzheimer’s disease and Parkinson’s disease model — a systematic review and meta-analysis.

Related Articles

Exercise effects on brain and behavior in healthy mice, Alzheimer’s disease and Parkinson’s disease model — a systematic review and meta-analysis.

Behav Brain Res. 2020 Jan 25;112488
Authors: da Costa Daniele TM, de Bruin PFC, de Matos RS, de Bruin GS, Maia Chaves Junior C, de Bruin VMS
Abstract
This systematic review and meta-analysis examines how exercise modifies brain and behavior in healthy mice, dementia (D) and Parkinson disease (PD) models. A search was performed on the Medline and Scopus electronic databases (2008 to 2019). Search terms were “mice”, “brain”, “treadmill”, “exercise”, “physical exercise”. In the total, 430 were found but only 103 were included. Animals (n = 1,172; 96 articles) exercised 4–8 weeks (Range 24 h to 32 weeks), 60 min/day (Range 8 to 120 min per day), and 10/12 m/min (Range 0.2 m/min to 36 m/min). Hippocampus, cerebral cortex, striatum and whole brain were more frequently investigated. Exercise improved learning and memory. Meta-analysis showed that exercise increased: cerebral BDNF in health (n = 150; z = 5.8, CI 3.43−12.05; p = 0.00000002).

PMID: 31991178 [PubMed — as supplied by publisher]

The protective and therapeutic effects of vinpocetine, a PDE1 inhibitor, on oxidative stress and learning and memory impairment induced by an intracerebroventricular (ICV) injection of amyloid beta (Aβ) peptide.

Related Articles

The protective and therapeutic effects of vinpocetine, a PDE1 inhibitor, on oxidative stress and learning and memory impairment induced by an intracerebroventricular (ICV) injection of amyloid beta (Aβ) peptide.

Behav Brain Res. 2020 Jan 25;112512
Authors: Shekarian M, Komaki A, Shahidi S, Sarihi A, Salehi I, Raoufi S
Abstract
Alzheimer’s disease (AD) is a neurodegenerative disease leading to cognitive and memory impairment. This study aimed at investigating the therapeutic and preserving effects of vinpocetine on amyloid beta (Aβ)-induced rat model of AD. Sixty male adult Wistar rats were randomly divided into 6 groups (n = 10 per group) as follows: 1; control, 2; sham, 3; Aβ, 4; pre-treatment (vinpocetine + Aβ); oral gavage administration of vinpocetine at 4 mg/kg for 30 days followed by intracerebroventricular (ICV) injection of Aβ, 5; treatment (Aβ + vinpocetine): Aβ ICV injection followed by vinpocetine administration for 30 days, 6; pre-treatment + treatment (vinpocetine + Aβ + vinpocetine): vinpocetine administration for 30 days before and 30 days after AD induction. Following treatments, the animals’ learning and memory were investigated using passive avoidance learning (PAL) task, Morris water maze (MWM), and novel object recognition (NOR) tests. The results demonstrated that Aβ significantly enhanced escape latency and the distance traveled in the MWM, decreased step-through latency, and increased time spent in the dark compartment in PAL. Vinpocetine ameliorated the Aβ-infused memory deficits in both MWM and PAL tests. Administration of vinpocetine in the Aβ rats increased the discrimination index of the NOR test. It also significantly diminished the nitric oxide and malondialdehyde levels and restored the reduced glutathione (GSH) levels. Vinpocetine can improve memory and learning impairment following Aβ infusion due to its different properties, including antioxidant effects, which indicates that vinpocetine administration can lead to the amelioration of cognitive dysfunction in AD.

PMID: 31991177 [PubMed — as supplied by publisher]

Glomerular hyperfiltration is associated with dementia: A nationwide population-based study.

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Glomerular hyperfiltration is associated with dementia: A nationwide population-based study.

Abstract
BACKGROUND: Glomerular hyperfiltration may be a clinical phenotype of endothelial dysfunction. Endothelial dysfunction may cause vascular dementia through the deterioration of cerebral blood flow. We aimed to identify the risk of dementia in people with glomerular hyperfiltration.

METHODS: Using the Korean National Health Information Database, we included subjects aged ≥45 years who underwent national health screening examinations between 2012 and 2015 and who had no previous history of end-stage renal disease or
dementia (n = 2,244,582). The primary exposure was glomerular hyperfiltration. We divided the subjects into groups by sex and five-year age intervals and categorized each group into 8 intervals according to estimated glomerular filtration (eGFR). The subjects with an eGFR ≥95th percentile in each group were defined as the hyperfiltration group. The outcomes were development of all types of dementia, Alzheimer’s dementia and vascular dementia. Multivariable Cox proportional hazards models were used to analyze the hazard ratios (HRs) for outcomes.

RESULTS: The Hyperfiltration group showed a higher risk for the development of all types of dementia [adjusted HR 1.09 (95% CI, 1.03–1.15)] and vascular dementia [adjusted HR 1.33 (95% CI, 1.14–1.55)] than the reference group. However, the association between hyperfiltration and Alzheimer’s dementia was not statistically significant.

CONCLUSIONS: Glomerular hyperfiltration may be associated with dementia. In this respect, subjects with glomerular hyperfiltration should be monitored more closely for signs and symptoms of dementia.

PMID: 31990949 [PubMed — in process]

Alzheimer Disease and Cancer: A National Inpatient Sample Analysis.

Related Articles

Alzheimer Disease and Cancer: A National Inpatient Sample Analysis.

Alzheimer Dis Assoc Disord. 2020 Jan 27:;
Authors: Sherzai AZ, Parasram M, Haider JM, Sherzai D

Abstract

INTRODUCTION: Studies have demonstrated an inverse relationship between Alzheimer dementia (AD) and cancer. This inverse relationship was further explored. In addition, Pin1 expression has been implicated in the cell cycle regulation of both disease processes. The relationship of Pin1 expression in 10 cancer types and secondary diagnosis of AD was examined.

MATERIALS AND METHODS: A cross-sectional analysis was performed using discharge data from the National Inpatient Sample from 1999 to 2008. Cancer was defined as the primary discharge diagnosis and AD was defined as the secondary discharge diagnosis. Cancer types were grouped according to their Pin1 expression to examine its relationship with AD. Analysis was performed by logistic regression.

RESULTS: Of ∼ 3 million cancer discharge diagnoses, 1.0% had a secondary diagnosis of AD. Discharge data of all 10 cancer types revealed a lower likelihood of secondary AD diagnosis. Prostate cancer [crude odds ratios (OR): 0.26 (0.24 to 0.29), multivariate OR: 0.39 (0.33 to 0.43)], ovarian cancer [crude OR: 0.38 (0.32 to 0.44), multivariate OR: 0.35 (0.30 to 0.41)], and lung cancer [crude OR: 0.39 (0.36 to 0.41), multivariate OR: 0.41 (0.39 to 0.44)] demonstrated the lowest odds of secondary AD diagnosis. When cancer types were grouped per Pin1 expression, cancer types with Pin1 underexpression were more likely to be associated with secondary diagnosis of AD than cancer types with Pin1 overexpression [crude OR: 1.4 (1.3 to 1.4), multivariate OR: 1.08 (1.02 to 1.14)].

DISCUSSION: This secondary data analysis further demonstrated an inverse relationship between AD and 10 cancer types, with prostate, ovarian, and lung cancers displaying the greatest inverse relationship. Pin1 underexpressing cancer types had a significantly higher likelihood of secondary diagnosis of AD than Pin1 overexpressing cancer types.

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Plasma tau protein and Aβ42 level as markers of cognitive impairment in patients with Parkinson’s disease.

Related Articles

Plasma tau protein and Aβ42 level as markers of cognitive impairment in patients with Parkinson’s disease.

Authors: Chojdak-Łukasiewicz J, Malodobra-Mazur M, Zimny A, Noga L, Paradowski B

Abstract

BACKGROUND: Parkinson’s disease (PD) is a progressive neurodegenerative disorder with a characteristic clinical picture. Apart from classical movement disorders, a significant role is also played by non-motor symptoms, in particular cognitive impairments, which have a significant impact on the quality of life of the patients. Tau protein and amyloid beta are well-known non-specific biomarkers in Alzheimer’s disease (AD).

OBJECTIVES: The study assessed the practical value of determining tau protein and amyloid beta (Aβ42) in the blood serum of patients with PD and their relationship with cognitive impairments, radiographic image and the used dose of L-DOPA.

MATERIAL AND METHODS: The neuropsychological assessment was carried for 64 patients with PD. The levels of amyloid beta 1–42 (Aβ42) and tau proteins in serum were also measured.

RESULTS: The Aβ42 level in the serum was statistically higher in patients with longer duration of the disease (p < 0.05). Tau protein and amyloid beta were well-known non-specific biomarkers in Alzheimer’s disease (AD).

CONCLUSIONS: Plasma tau protein and Aβ42 level as markers of cognitive impairment in patients with Parkinson’s disease.

PMID: 31990459 [PubMed — as supplied by publisher]

Guanidine hydrochloride reactsivates an ancient septin hetero-oligomer assembly pathway in budding yeast.

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Guanidine hydrochloride reactsivates an ancient septin hetero-oligomer assembly pathway in budding yeast.

Elife. 2020 Jan 28:;
Authors: Johnson CR, Steingesser MG, Weems AD, Khan A,
Alzheimer’s Disorder: Epigenetic connection and associated risk factors.

Related Articles

Alzheimer’s Disorder: Epigenetic connection and associated risk factors.

Curr Neuropharmacol. 2020 Jan 28:;

Authors: Sharma VK, Mehta V, Singh TG

Abstract

The gene based therapeutics and drug targets have shown incredible and appreciable advances in alleviating human sufferings and complexities. Epigenetics simply means above genetics or which controls the organism beyond genetics. At present it is very clear that all characteristics of an individual are not determined by DNA alone, rather the environment, stress, lifestyle and nutrition play a vital part in determining the response of an organism. Thus nature (genetic makeup) and nurture (exposure) play equally important roles in the responses observed, both at the cellular and organism levels. Epigenetics influence plethora of complications at cellular and molecular levels that includes cancer, metabolic and cardiovascular complications including neurological (psychosis) and neurodegenerative disorders (Alzheimer’s disease, Parkinson disease etc.). The epigenetic mechanisms include DNA methylation, histone modification and non coding RNA which have substantial impact on progression and pathways linked to Alzheimer’s disease. The epigenetic mechanism get deregulated in Alzheimer’s disease and is characterized by DNA hyper methylation, deacetylation of histones and general repressed chromatin state which alter gene expression at transcription level by upregulation, downregulation

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Related Network and Differential Expression Analyses Identify Nuclear Genes and Pathways in the Hippocampus of Alzheimer Disease.

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Related Network and Differential Expression Analyses Identify Nuclear Genes and Pathways in the Hippocampus of Alzheimer Disease.

Med Sci Monit. 2020 Jan 28;26:e919311

Authors: Quan X, Liang H, Chen Y, Qin Q, Wei Y, Liang Z

Abstract

BACKGROUND Alzheimer disease (AD) is a typical progressive and destructive neurodegenerative disease that has been studied extensively. However, genetic features and molecular mechanisms underlying AD remain unclear. Here we used bioinformatics to investigate the candidate nuclear genes involved in the molecular mechanisms of AD. MATERIAL AND METHODS First, we used Gene Expression Omnibus (GEO) database to obtain the expression profiles of the mRNAs from hippocampus microarray and identify differentially expressed genes (DEGs) the plier algorithm. Second, functional annotation and visualization of the DEGs were conducted by the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. Finally, BioGRID, IntAct, STRING, and Cytoscape were utilized to construct a protein-protein interaction (PPI) network. Hub genes were analytically obtained from the PPI network and the microRNA (miRNA)-target network. RESULTS Two hippocampus microarrays (GSE5281 and GSE48350) were obtained from the GEO database, comprising 161 and 253 cases separately. Among these, 118 upregulated genes and 694 downregulated genes were identified. The upregulated DEGs were mainly involved in positive regulation of transcription from RNA polymerase II promoter, positive regulation of cartilage development, and response to wounding. The downregulated DEGs were enriched in chemical synaptic transmission, neurotransmitter secretion, and learning. By combining the results of PPI and miRNA-target network, 8 genes and 2 hub miRNAs were identified, including YWHAZ, DLG4, AGAP2, EGFR, TGFBR3, PSD3, RDX, BRWD1, and hsa-miR-106b-5p and hsa-miR-93-5p. These target genes are highly enriched in various key pathways, such as amyloid-beta formation, regulation of cardiocyte differentiation, and actin cytoskeleton reorganization. CONCLUSIONS In this study, YWHAZ, DLG4, AGAP2, EGFR, TGFBR3, PSD3, RDX, and BRWD1 were identified as candidate genes for future molecular studies in AD, which is expected to improve our understanding of its cause and potential molecular mechanisms. Nuclear genes, DEGs, and related networks identified by integrated bioinformatics analysis may serve as diagnostic and therapeutic targets for AD.
or silencing of genes. Thus the processes or modulators of these epigenetic processes have shown vast potential as therapeutic target in Alzheimer’s disease.

PMID: 31989902 [PubMed — as supplied by publisher]


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Curr Neuropharmacol. 2020 Jan 28;:
Authors: Singh RK

Abstract
Alzheimer’s disease is one of the most progressive forms of dementia ultimately leading to death in aged populations. The major hallmarks of Alzheimer’s disease include deposition of extracellular amyloid senile plaques and intracellular neurofibrillary tangles in brain neuronal cells. Although there are classical therapeutic options available for the treatment of the diseases, however they provide only a symptomatic relief and do not modify the molecular pathophysiological course of the disease. Recent research advances on Alzheimer’s disease have highlighted a potential role of anti-amyloid, anti-tau and anti-inflammatory therapies. However, these therapies are still in different phases of pre-clinical/clinical development. In addition, drug repositioning/repurposing is another interesting and promising approach to explore rationalized options for treatment of Alzheimer’s disease. This review discusses about the different aspect of pathophysiological mechanism involved in progression of Alzheimer’s disease along with the limitations of the current therapies. Furthermore, this review also highlights emerging investigational drugs along with recent drug repurposing approaches for Alzheimer’s disease.

PMID: 31989900 [PubMed — as supplied by publisher]

Convolutional Neural Network-based MR Image Analysis for Alzheimer’s Disease Classification.

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Convolutional Neural Network-based MR Image Analysis for Alzheimer’s Disease Classification.

Curr Med Imaging Rev. 2020;16(1):27–35
Authors: Choi BK, Madusanka N, Choi HK, So JH, Kim CH, Park HG, Bhattacharjee S, Prakash D

Abstract
BACKGROUND: In this study, we used a convolutional neural network (CNN) to classify Alzheimer’s disease (AD), mild cognitive impairment (MCI), and normal control (NC) subjects based on images of the hippocampus region extracted from magnetic resonance (MR) images of the brain.

METHODS: The datasets used in this study were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI). To segment the hippocampal region automatically, the patient brain MR images were matched to the International Consortium for Brain Mapping template (ICBM) using 3D-Slicer software. Using prior knowledge and anatomical annotation label information, the hippocampal region was automatically extracted from the brain MR images.

RESULTS: The area of the hippocampus in each image was preprocessed using local entropy minimization with a bi-cubic spline model (LEMS) by an inhomogeneity intensity correction method. To train the CNN model, we separated the dataset into three groups, namely AD/NC, AD/MCI, and MCI/NC. The prediction model achieved an accuracy of 92.3% for AD/NC, 85.6% for AD/MCI, and 78.1% for MCI/NC.

CONCLUSION: The results of this study were compared to those of previous studies, and summarized and analyzed to facilitate more flexible analyses based on additional experiments. The classification accuracy obtained by the proposed method is highly accurate. These findings suggest that this approach is efficient and may be a promising strategy to obtain good AD, MCI and NC classification performance using small patch images of hippocampus instead of whole slide images.

PMID: 31988891 [PubMed — in process]

The danger of being too sympathetic: norepinephrine in Alzheimer’s Disease and greying of hair.

Related Articles

The danger of being too sympathetic: norepinephrine in Alzheimer’s Disease and greying of hair.

Rejuvenation Res. 2020 Jan 28;:
Authors: Mendelsohn AR, Larrick J

Abstract
Although alterations in the sympathetic nervous system (SNS) with age have been reported and serious degenerative diseases of the autonomic nervous system like multiple system atrophy are more likely to strike older people, connections between dysregulated adrenergic receptors and age-associated diseases and phenotypes have not been well-studied. Two recent reports suggest that SNS may be more closely connected than previously appreciated. First, low nanomolar concentrations of Alzheimer’s disease (AD)-associated Aβ42 amyloid oligomers alter signaling by SNS neurotransmitter norepinephrine (NE) to sufficiently activate kinase GSK3β to hyperphosphorylate tau, a key mediator of neurotoxicity in AD. Connecting beta amyloid to tau in AD has
been a key quest in understanding AD and developing therapeutics. The α2 adrenergic receptor inhibitory drug idazoxan reduces GSK3β activity and tau phosphorylation in AD mice with improved cognitive function, even in the presence of beta amyloid deposits. Here, SNS activation in the brain coupled with problematic Aβ42 amyloid oligomers result in serious consequences that can be ameliorated by reducing SNS signaling. A second example of the detrimental effects of increased SNS signaling is the premature of greying of hair in response to stress. Secretion of NE resulting from stress causes differentiation of most hair pigment melanocyte stem cells (MeSCs) into melanocytes, rapidly depleting the hair follicle of pigment-producing cells as mature melanocytes undergo apoptosis and MeSCs are eventually eliminated. Blockade of NE SNS signaling preserves hair coloration in stressed animals. Increased SNS activation has serious, apparently irreversible effects on homeostasis in both situations. Although neither report directly addresses aging, given that AD and the loss of hair pigmentation have strong age-associations, it is of interest to better understand the role that SNS has in promoting age-associated phenotypes generally and determine if tuning the SNS through drug-mediated attenuation of SNS signaling may be of medical benefit.

PMID: 31989871 [PubMed — as supplied by publisher]

Sodium tanshinone IIA sulfonate protects against Aβ-induced cell toxicity through regulating Aβ process.

Related Articles

Sodium tanshinone IIA sulfonate protects against Aβ-induced cell toxicity through regulating Aβ process.

J Cell Mol Med. 2020 Jan 27;

Authors: Zhang DP, Lu XY, He SC, Li WY, Ao R, Leung FC, Zhang ZM, Chen QB, Zhang SJ

Abstract

Sodium tanshinone IIA sulfonate (STS) has been reported to prevent Alzheimer’s disease (AD). However, the mechanism is still unknown. In this study, two in vitro models, Aβ-treated SH-SY5Y cells and SH-SY5Y human neuroblastoma cells transfected with APPsw (SH-SY5Y APPsw cells), were employed to investigate the neuroprotective of STS. The results revealed that pretreatment with STS (1, 10 and 100 µmol/L) for 24 hours could protect against Aβ (10 µmol/L)-induced cell toxicity in a dose-dependent manner in the SH-SY5Y cells. Sodium tanshinone IIA sulfonate decreased the concentrations of reactive oxygen species, malondialdehyde, NO and iNOS, while increased the activities of superoxide dismutase and glutathione peroxidase in the SH-SY5Y cells. Sodium tanshinone IIA sulfonate decreased the levels of inflammatory factors (IL-1β, IL-6 and TNF-α) in the SH-SY5Y cells. In addition, Western blot results revealed that the expressions of neprilysin and insulin-degrading enzyme were up-regulated in the SH-SY5Y cells after STS treatment. Furthermore, ELISA and Western blot results showed that STS could decrease the levels of Aβ. ELISA and qPCR results indicated that STS could increase α-secretase (ADAM10) activity and decrease β-secretase (BACE1) activity. In conclusion, STS could protect against Aβ-induced cell damage by modulating Aβ degration and generation. Sodium tanshinone IIA sulfonate could be a promising candidate for AD treatment.

PMID: 31989795 [PubMed — as supplied by publisher]

Frontal variant of Alzheimer’s disease with asymmetric presentation mimicking frontotemporal dementia: Case report and literature review.

Related Articles

Frontal variant of Alzheimer’s disease with asymmetric presentation mimicking frontotemporal dementia: Case report and literature review.

Brain Behav. 2020 Jan 27;e01548

Authors: Li CH, Fan SP, Chen TF, Chiu MJ, Yen RF, Lin CH

Abstract

INTRODUCTION: Frontal variant of Alzheimer’s disease (fvAD) is a rare nonamnestic syndrome of Alzheimer’s disease (AD). Differentiating it from behavior variant of frontotemporal dementia (bvFTD), which has implications for treatment responses and prognosis, remains a clinical challenge. METHODS: Molecular neuroimaging and biofluid markers were performed for the index patient for accurate premortem diagnosis of fvAD. The clinical, neuroimaging, and biofluid characteristics of the patient were compared to those reported in previous studies of fvAD from 1999 to 2019. RESULTS: A 66-year-old man presented with progressive executive dysfunction, personality and behavioral changes, and memory decline since age 59. He had no family history of neurodegenerative disorders. A stimulus-sensitive myoclonus was noted over his left upper extremity. Neuropsychological assessment revealed moderate dementia with a Mini-Mental State Exam score of 10/30 and compromised executive and memory performance. Brain imaging showed asymmetrical atrophy and hypometabolism over the right frontal and temporal areas, mimicking bvFTD. However, we observed increased tau depositions based on 18 F-labeled T807 Tau PET in these areas and diffusely increased amyloid deposition based on 11 C-labeled Pittsburgh compound B positron emission tomography (PET). Plasma biomarker measures indicated an AD profile with increased Aβ1-42 (18.66 pg/ml; cutoff: 16.42 pg/ml), Aβ1-42/Aβ1-40 ratio (0.45; cutoff: 0.30), total tau (29.78 pg/ml; cutoff: 23.89 pg/ml), and phosphorylated tau (4.11 pg/ml; cutoff: 3.08 pg/ml). These results supported a diagnosis of fvAD. CONCLUSIONS: Our results with asymmetrical presentations extend current knowledge about this rare AD variant. Application of biofluid and molecular imaging markers could assist in early, accurate diagnosis.
Salivary biomarkers in Alzheimer’s disease.

Related Articles

**Salivary biomarkers in Alzheimer’s disease.**

Clin Oral Investig. 2020 Jan 27;:

Authors: Tvarijonaviciute A, Zamora C, Ceron JJ, Bravo-Cantero AF, Pardo-Marin L, Valverde S, Lopez-Jornet P

Abstract

OBJECTIVES: The objective of this study was to evaluate the changes that can occur in saliva components in patients with Alzheimer’s disease (AD) of different severity and determine if any of these components could be a biomarker of this disease. Therefore, a panel of selected analytes related to the amyloid cascade, the immune and adrenergic systems, among others, were analyzed in the saliva of patients with Alzheimer’s disease.

METHODS: A total of 152 patients with AD and controls were included. The severity of the disease was established according to the Global Deterioration Scale. Unstimulated whole saliva was collected.

RESULTS: Salivary amyloid-β42 was significantly lower, and complement C4 was significantly higher in the patients with AD than in the controls (p

**CONCLUSIONS:** A decrease in amyloid-β42 and an increase in complement C4 were detected in the saliva of patients with AD, but the changes did not show a high diagnostic performance for the detection of AD and were not associated with its severity.

CLINICAL RELEVANCE: Although some analytes showed significant differences in saliva in patients with AD, in our study conditions the salivary biomarkers analyzed were not of enough diagnostic utility for being used in routine.

Blood and brain gene expression trajectories mirror neuropathology and clinical deterioration in neurodegeneration.

Related Articles

**Blood and brain gene expression trajectories mirror neuropathology and clinical deterioration in neurodegeneration.**

Brain. 2020 Jan 28;:

Authors: Iturria-Medina Y, Khan AF, Adewale Q, Shirazi AH, Alzheimer’s Disease Neuroimaging Initiative

Abstract

Most prevalent neurodegenerative disorders take decades to develop and their early detection is challenged by confounding non-pathological ageing processes. For all neurodegenerative conditions, we continue to lack longitudinal gene expression data covering their large temporal evolution, which hinders the understanding of the underlying dynamic molecular mechanisms. Here, we overcome this key limitation by introducing a novel gene expression contrastive trajectory inference (GE-cTI) method that reveals enriched temporal patterns in a diseased population. Evaluated on 1969 subjects in the spectrum of late-onset Alzheimer’s and Huntington’s diseases (from ROspmAP, HBTRC and ADNI datasets), this unsupervised machine learning algorithm strongly predicts neuropathological severity (e.g. Braak, amyloid and Vonsattel stages). Furthermore, when applied to in vivo blood samples at baseline (ADNI), it significantly predicts clinical deterioration and conversion to advanced disease stages, supporting the identification of a minimally invasive (blood-based) tool for early clinical screening. This technique also allows the discovery of genes and molecular pathways, in both peripheral and brain function. Autophagy is documented as a defining feature of neurodegeneration in Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HD). In the present study, we found that BGN protected neuronal cells from nitric oxide (NO)-induced cell apoptosis. However, it is still unclear that whether the neuroprotective effect of BGN relates to autophagy. Here, we discovered that an NO donor, sodium nitroprusside (SNP) induced autophagy in human SH-SY5Y neuroblastoma cells, including activating LC3B and inhibiting p62. Inhibiting autophagy by 3MA aggravated NO-induced cell death, otherwise promoting autophagy by Rapamycin rescued NO-triggered cell death. Notably, BGN downregulated by NO, significantly protected SH-SY5Y cells against NO-induced neurotoxicity by inhibiting the activation of autophagy-dependent AMPK signaling pathway. Moreover, BGN overexpression also diminished NO-induced the elevation of intracellular reactive oxygen species (ROS) level, but not NO content. These findings suggest that BGN protects neuroblastoma cells from NO-induced death by suppressing autophagy-dependent AMPK-mTOR signaling and intracellular ROS level.

Biglycan protects human neuroblastoma cells from nitric oxide-induced death by inhibiting AMPK-mTOR mediated autophagy and intracellular ROS level.

Related Articles

**Biglycan protects human neuroblastoma cells from nitric oxide-induced death by inhibiting AMPK-mTOR mediated autophagy and intracellular ROS level.**

Biotechnol Lett. 2020 Jan 27;:

Authors: Chen S, Guo D, Lei B, Bi J, Yang H

Abstract

The ubiquitous proteoglycan, biglycan (BGN) acts as an important modulator, regulating key molecular pathways of metabolism and
brain tissues, that are highly predictive of disease evolution. Eighty-five to ninety per cent of the most predictive molecular pathways identified in the brain are also top predictors in the blood. These pathways support the importance of studying the peripheral-brain axis, providing further evidence for a key role of vascular structure/functioning and immune system response. The GE-cTI is a promising tool for revealing complex neuropathological mechanisms, with direct implications for implementing personalized dynamic treatments in neurology.

PMID: 31989163 [PubMed — as supplied by publisher]

Kinetic and thermodynamic study of beta-Boswellic acid interaction with Tau protein investigated by surface plasmon resonance and molecular modeling methods.

Related Articles
Kinetic and thermodynamic study of beta-Boswellic acid interaction with Tau protein investigated by surface plasmon resonance and molecular modeling methods.

Bioimpacts. 2020;10(1):17-25


Abstract
Introduction: Beta-Boswellic acid (BBA) is a pentacyclic terpene which has been obtained from frankincense and its beneficial effects on neurodegenerative disorders such as Alzheimer’s disease (AD) have been addressed. Methods: In the present study, thermodynamic and kinetic aspects of BBA interaction with Tau protein as one of the important proteins involved in AD in the absence and presence of glucose has been investigated using surface plasmon resonance (SPR) method. Tau protein was immobilized onto the carboxy methyl dextran chip and its binding interactions with BBA were studied at physiological pH at various temperatures. Glucose interference with these interactions was also investigated. Results: Results showed that BBA forms a stable complex with Tau (KD=8.45×10−7 M) at 298 K. Molecular modeling analysis showed a hydrophobic interaction between BBA and HVPGGG segment of R2 and R4 repeated domains of Tau. Conclusion: The binding affinity increased by temperature enhancement, while it decreased significantly in the presence of glucose. Both association and dissociation of the BBA-Tau complex were accompanied with an entropic activation barrier; however, positive enthalpy and entropy changes revealed that hydrophobic bonding is the main force involved in the interaction.

PMID: 31988853 [PubMed]

Effect of the micro-environment on α-synuclein conversion and implication in seeded conversion assays.

Related Articles
Effect of the micro-environment on α-synuclein conversion and implication in seeded conversion assays.

Transl Neurodegener. 2020;9:5


Abstract
Background: α-Synuclein is a small soluble protein, whose physiological function in the healthy brain is poorly understood. Intracellular inclusions of α-synuclein, referred to as Lewy bodies (LBs), are pathological hallmarks of α-synucleinopathies, such as Parkinson’s disease (PD) or dementia with Lewy bodies (DLB). Main body: Understanding of the molecular basis as well as the factors or conditions promoting α-synuclein misfolding and aggregation is an important step towards the comprehension of pathological mechanism of α-synucleinopathies and for the development of efficient therapeutic strategies. Based on the conversion and aggregation mechanism of α-synuclein, novel diagnostic tests, such as protein misfolding seeded conversion assays, e.g. the real-time quaking-induced conversion (RT-QuIC), had been developed. In diagnostics, α-synuclein RT-QuIC exhibits a specificity between 82 and 100% while the sensitivity varies between 70 and 100% among different laboratories. In addition, the α-synuclein RT-QuIC can be used to study the α-synuclein-seeding-characteristics of different α-synucleinopathies and to differentiate between DLB and PD. Conclusion: The variable diagnostic accuracy of current α-synuclein RT-QuIC occurs due to different protocols, cohorts and material etc.. An impact of micro-environmental factors on the α-synuclein aggregation and conversion process and the occurrence and detection of differential misfolded α-synuclein types or strains might underpin the clinical heterogeneity of α-synucleinopathies.

PMID: 31988747 [PubMed]

Structure and assembly of calcium homeostasis modulator proteins.

Related Articles
Structure and assembly of calcium homeostasis modulator proteins.

Nat Struct Mol Biol. 2020 Jan 27;
Simrowski N, Tucker SJ, Grigorieff N, Furukawa H

Abstract
The biological membranes of many cell types contain large-pore channels through which a wide variety of ions and metabolites permeate. Examples include connexin, innexin and pannexin, which form gap junctions and/or bona fide cell surface channels. The most recently identified large-pore channels are the calcium homeostasis modulators (CALHMs), through which ions and ATP permeate in a voltage-dependent manner to control neuronal excitability, taste signaling and pathologies of depression and Alzheimer’s disease. Despite such critical biological roles, the structures and patterns of their oligomeric assembly remain unclear. Here, we reveal the structures of two CALHMs, chicken CALHM1 and human CALHM2, by single-particle cryo-electron microscopy (cryo-EM), which show novel assembly of the four transmembrane helices into channels of octamers and undecamers, respectively. Furthermore, molecular dynamics simulations suggest that lipids can favorably assemble into a bilayer within the larger CALHM2 pore, but not within CALHM1, demonstrating the potential correlation between pore size, lipid accommodation and channel activity.

PMID: 31988524 [PubMed — as supplied by publisher]

T cells on patrol in Alzheimer disease.

Related Articles
T cells on patrol in Alzheimer disease.
Nat Rev Neurol. 2020 Jan 27;;
Authors: Lemptrière S
PMID: 31988485 [PubMed — as supplied by publisher]

Regional and temporal miRNAs expression profile in a transgenic mouse model of tauopathy: implication for its pathogenesis.

Related Articles
Regional and temporal miRNAs expression profile in a transgenic mouse model of tauopathy: implication for its pathogenesis.
Mol Psychiatry. 2020 Jan 27;;
Authors: Lauretti E, Dincer O, Praticò D
Abstract
Studies have shown that the expression level of different microRNAs (miRNAs) is altered in neurodegenerative disorders including tauopathies, a group of diseases pathologically defined by accumulation of tau protein in neurons and glia cells. However, despite this evidence we still do not know whether miRNA changes precede their onset, thus potentially contributing to the pathogenesis, or are downstream events secondary to tau pathology. In the current paper, we assessed the miRNA expression profile at different age time points and brain regions in a relevant mouse model of human tauopathy, the hTau mice, in relationship with the development of behavioral deficits and tau neuropathology. Compared with age-matched control, four specific miRNAs (miR-132-3p, miR-146a-5p, miR-22-3p, and miR-455-5p) were found significantly upregulated in 12-month-old hTau mice. Interestingly, three of them (miR-132-3p, miR-146a-5p, and miR-22-3p) were already increased in 6-month-old mice, an age before the development of tau pathologic phenotype. Investigation of their predicted targets highlighted pathways relevant to neuronal survival and synaptic function. Collectively, our findings support the new hypothesis that in tauopathies the change in the expression level of specific miRNAs is an early event and plays a functional role in the pathogenesis of the diseases by impacting several mechanisms involved in the development of the associated neuropathology.

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Depressive-like phenotype evoked by lifelong nutritional omega-3 deficiency in female rats: crosstalk among kynurenine, Toll-like receptors and amyloid beta oligomers.

Related Articles
Depressive-like phenotype evoked by lifelong nutritional omega-3 deficiency in female rats: crosstalk among kynurenine, Toll-like receptors and amyloid beta oligomers.
Brain Behav Immun. 2020 Jan 24;;
Authors: Grazia Morgese M, Schiavone S, Bruna Maffione A, Tucci P, Trabace L
Abstract
Depression is one of the most common psychiatric diseases and the prevalence of depressive symptoms in women is almost twice compared to men, although the reasons of this gender difference are not fully understood yet. Recently, soluble amyloid beta (Aβ)1–42 peptide has been receiving great importance in the development of depression, also considering that depression is highly comorbid with Alzheimer’s disease and other neurodegenerative illnesses. The central role played by Aβ in the development of depressive-like symptoms in rodents has been evidenced in environmental rodent model of depression. Indeed, we have previously found that lifelong exposure to n-3 polyunsaturated fatty acids (PUFA) deficient diet in female rats at 8 weeks of life leads to depressive like- symptoms and higher susceptibility to stress associated with increased Aβ levels. In order to understand if such effects were maintained over time, rats were exposed to the same diet regimen until 6 or 21 weeks of life. We found that both timepoints of exposure to n-3 PUFA deficient...
diet lead to depressive-like phenotype. Furthermore, a significant alteration in brain neurochemistry was retrieved. In particular, in hippocampal area a significant reduction in serotonin (5-HT) and noradrenaline (NA) content was evidenced. Considering the prominent role of NA in counterbalancing neuroinflammatory state, we quantified in the same brain area kynurenine levels, a metabolite of tryptophan implicated in inflammatory state and brought to the fore for its implication in depression. Interestingly, kynurenine levels were significantly increased in hippocampus (HIPP) of female rats exposed to such diet. In addition, lifelong deficiency in n-3 PUFA dietary intake led to systemic increase of corticosterone, hence hypothalamic pituitary adrenal (HPA) axis hyperactivation, and higher proinflammatory cytokine production. Increased production of kynurenine, along with HPA axis hyperactivation, have been associated with immune system modulation, particularly through Toll-like receptor type 2 (TLR2) and Toll-like receptor type 4 (TLR4) involvement. In addition, it has been shown that soluble forms of Aβ1-42 can induce depressive-like phenotype in consequence to a crosstalk between TLR4 and 5-HTergic system. Thus, considering that in this model we have previously reported increased plasma Aβ1-42 level, we quantified TLR2 and 4 expression in HIPP of treated rats. We found that chronic exposure to a diet characterized by very low n-3 PUFA content led to higher expression of TLR2 and TLR4 in HIPP of female treated rats, indicating an activation of the immune system and was accompanied by increased expression of oligomeric Aβ. Taken together, our data indicate that the pro-depressive effects induced by a diet poor in n-3 PUFA can be attributable to a shift of hippocampal tryptophan metabolism toward inflammatory metabolite ultimately corresponding to altered immune response and increased Aβ oligomerization.

PMID: 31987923 [PubMed — as supplied by publisher]
Fatty acid metabolism in the progression and resolution of CNS disorders.

Related Articles

Fatty acid metabolism in the progression and resolution of CNS disorders.

Adv Drug Deliv Rev. 2020 Jan 24;:
Authors: Bogie JFJ, Haidar M, Kooij G, Hendriks JJA

Abstract
Recent advances in lipidomics and metabolomics have unveiled the complexity of fatty acid metabolism and the fatty acid lipidome in health and disease. A growing body of evidence indicates that imbalances in the metabolism and level of fatty acids drive the initiation and progression of central nervous system (CNS) disorders such as multiple sclerosis, Alzheimer’s disease, and Parkinson’s disease. Here, we provide an in-depth overview on the impact of the β-oxidation, synthesis, desaturation, elongation, and peroxidation of fatty acids on the pathophysiology of these and other neurological disorders. Furthermore, we discuss the impact of individual fatty acids species, acquired through the diet or endogenously synthesized in mammals, on neuroinflammation, neurodegeneration, and CNS repair. The findings discussed in this review highlight the therapeutic potential of modulators of fatty acid metabolism and the fatty acid lipidome in CNS disorders, and underscore the diagnostic value of lipidome signatures in these diseases.

PMID: 31987838 [PubMed — as supplied by publisher]

Cognitive improvement and synaptic deficit attenuation by a multifunctional carbazole-based cyanine in AD mice model through regulation of Ca2+/CaMKII/CREB signaling pathway.

Related Articles

Cognitive improvement and synaptic deficit attenuation by a multifunctional carbazole-based cyanine in AD mice model through regulation of Ca2+/CaMKII/CREB signaling pathway.

Exp Neurol. 2020 Jan 24;113210
Authors: Chen C, Xu D, Zhang ZH, Jia SZ, Cao XC, Chen YB, Song GL, Wong MS, Li HW

Abstract
Accumulation of β-amyloid (Aβ) peptide and hyperphosphorylated tau in the brain is one of the pathological characteristics of Alzheimer’s disease (AD) and attractive therapeutic targets in its treatment. In the present study, the cognitive ability of 4-month-old 3 × Tg-AD mice significantly improved after 40 days treatment with intraperitoneal injection of 2.25 mg/kg of SLOH, which is a multifunctional carbazole-based cyanine fluorophore. It reduced Aβ deposition, tau levels and its hyperphosphorylation by modulating AKT/glycogen synthase kinase-3β activities and promoting protein phosphatase 2A activity in the brain as well as in the primary neurons of 3 × Tg-AD mice. Moreover, SLOH attenuated synaptic deficit both in vitro and in vivo by regulating the Ca2+/CaMKII/CREB signaling pathway. These findings strongly suggest that SLOH owns a high therapeutic potential to treat early onset AD.

PMID: 31987831 [PubMed — as supplied by publisher]

Pregnancy, Postpartum and Parity: Resilience and Vulnerability in Brain Health and Disease.

Related Articles

Pregnancy, Postpartum and Parity: Resilience and Vulnerability in Brain Health and Disease.

Front Neuroendocrinol. 2020 Jan 24;100820
Authors: Deems N, Leuner B

Abstract
Risk and resilience in brain health and disease can be influenced by a variety of factors. While there is a growing appreciation to consider sex as one of these factors, far less attention has been paid to sex-specific variables that may differentially impact females such as pregnancy and reproductive history. In this review, we focus on nervous system disorders which show a female bias and for which there is data from basic research and clinical studies pointing to modification in disease risk and progression during pregnancy, postpartum and/or as a result of parity: multiple sclerosis (MS), depression, stroke, and Alzheimer’s disease (AD). In doing so, we join others (Shors, 2016; Galea et al., 2018) in aiming to illustrate the importance of looking beyond sex in neuroscience research.

PMID: 31987814 [PubMed — as supplied by publisher]

Stress and neurodegeneration.

Related Articles

Stress and neurodegeneration.

Clin Chim Acta. 2020 Jan 24;:
Authors: Peña-Bautista C, Casas-Fernández E, Vento M, Baquero M, Cháfer-Pericás C

Abstract
Neurodegenerative diseases are a great concern because of aging
Applications of biosensors in Alzheimer’s disease diagnosis.

Related Articles
Applications of biosensors in Alzheimer’s disease diagnosis.

Talanta. 2020 Apr 01;210:120644
Authors: Brazaca LC, Sampaio I, Zucolotto V, Janegitz BC

Abstract
Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by a progressive and irreversible cognitive decline. Currently, it affects 36 million people and due to population ageing it is estimated that in 2030 disease incidence will reach 60 million individuals. The precise diagnosis of AD is a complex task, being mainly performed by cerebrospinal fluid (CSF) analysis or neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI). Despite being effective these techniques are expensive, time-consuming and not accessible for most part of the population. In this scenario biosensors are presented as promising alternatives for simple, rapid and low cost diagnosis of AD. In this revision we summarize the recent advances on biosensors that brings more accessibility to AD diagnosis. We introduce the most used biorecognition elements in miniaturized biosensing systems as well as AD biomarkers present in CSF, plasma and in genetic material which can be used for disease identification even in early stages. The recent developed biosensors for AD diagnosis using optical, electrochemical and colorimetric techniques as well as their strategies and analytical performances are discussed. Advancements in signal amplification methodologies with nanomaterials to increase biosensors sensitivity are also presented. This review highlights the potential of biosensors to be used as an accurate and portable tool to improve the early AD diagnosis.

PMID: 31987795 [PubMed — as supplied by publisher]

Experimental and theoretical validations of a one-pot sequential sensing of Hg2+ and biothiols by a 3D Cu-based zwitterionic metal-organic framework.

Related Articles
Experimental and theoretical validations of a one-pot sequential sensing of Hg2+ and biothiols by a 3D Cu-based zwitterionic metal-organic framework.

Talanta. 2020 Apr 01;210:120596
Authors: Chen HL, Li RT, Wu KY, Hu PP, Zhang Z, Huang NH, Zhang WH, Chen JX

Abstract
A zwitterionic three-dimensional (3D) metal-organic framework (MOF) of \{(Cu(Cdcbp)(bipy))·4H2O\}n (1) has been synthesized and characterized (H3CdcbpBr = 3-carboxyl-(3,5-dicarboxybenzyl)-pyridinium bromide; bipy = 4,4′-bipyridine). MOF 1 exhibits a variety of structural traits, such as ligand conjugated, positively charged pyridinium center, and Cu(II) cations that collectively enable its efficient hybridization with the flexible, negatively charged, single-stranded, and thymine-rich (T-rich) DNA. The T-rich DNA is labeled with carboxyfluorescein (FAM) fluorescent probe (characterized as P-DNA), but the resultant MOF 1 — P-DNA hybrid (characterized as P-DNA@1) is non-emissive (off-state) because of the fluorescent quenching by MOF 1. The P-DNA@1 hybrid functions as an effective and selective sensor for Hg2+ due to the formation of rigid hairpin-like T-Hg2+-T double-stranded DNA (ds-DNA@Hg2+) which is subsequently ejected by MOF 1, triggering a recovery of the P-DNA fluorescence (on-state). Subsequent addition of biothiols further sequestrates Hg2+ from the ds-DNA@Hg2+ duplex driven by the stronger Hg-S coordination, thus release the P-DNA and, in turn, resolved by MOF 1 to regain the initial hybrid (off-state). P-DNA@1 hybrid thus detects Hg2+ and biothiols sequentially via a fluorescence “off-on” mechanism. The limits of detection (LOD) for Hg2+, biothiols, including cysteine (Cys), glutathione (GSH) and homocysteine (Hcy) are 3.0, 14.2, 15.1 and 8.0 nM, respectively, with the detection time of 60 min for Hg2+, and instantaneous detection for all the three biothiols. The detection mechanism is further confirmed by circular dichroism (CD), fluorescence anisotropy (FA), binding constant and molecular simulation. This sequential detection of Hg2+ and biothiols counter-proofs the presence of each other and may shed light to the occurrence of related diseases, such as neurodegenerative disorders of Parkinson’s disease (PD), and Alzheimer’s disease (AD).

PMID: 31987206 [PubMed — in process]
Effects of neural stem cell transplantation in Alzheimer’s disease models.

**Related Articles**

Effects of neural stem cell transplantation in Alzheimer’s disease models.


Authors: Hayashi Y, Lin HT, Lee CC, Tsai KJ

**Abstract**

Currently there are no therapies for treating Alzheimer’s disease (AD) that can effectively halt disease progression. Existing drugs such as acetylcholinesterase inhibitors or NMDA receptor antagonists offers only symptomatic benefit. More recently, transplantation of neural stem cells (NSCs) to treat neurodegenerative diseases, including AD, has been investigated as a new therapeutic approach. Transplanted cells have the potential to replace damaged neural circuitry and secrete neurotrophic factors to counter symptomatic deterioration or to alter lesion protein levels. However, since there are animal models that can recapitulate AD in its entirety, it is challenging to precisely characterize the positive effects of transplanting NSCs. In the present review, we discuss the types of mouse modeling system that are available and the effect in each model after human-derived NSC (hNSC) or murine-derived NSC (mNSC) transplantation. Taken together, results from studies involving NSC transplantation in AD models indicate that this strategy could serve as a new therapeutic approach.

PMID: 31987051 [PubMed — in process]

Mild pericyte deficiency is associated with aberrant brain microvascular flow in aged PDGFRβ+/- mice.

**Related Articles**

Mild pericyte deficiency is associated with aberrant brain microvascular flow in aged PDGFRβ+/- mice.

*J Cereb Blood Flow Metab*. 2020 Jan 27;271678X19900543

Authors: Watson AN, Berthiaume AA, Faino AV, McDowell KP, Bhat NR, Hartmann DA, Shih AY

**Abstract**

Introduction: Mitochondria (mt) are protein-protein interaction (PPI) hubs in the cell where mt-localized and mt-associated proteins imported from the cytosol interact in a fashion that is critical for cell fitness and fate. Altered mtPPIs are linked to neurodegenerative disorders (NDs) and act as drivers of pathological associations to mediate ND progression. Mapping these altered mtPPIs will reveal how mt dysfunction is linked to NDs.Areas covered: This review discusses how different database sources reflect on the number of mt protein or interaction predictions, and serves as an update on mtPPIs involved in mt dynamics and homeostasis. Emphasis is given to mRNA expression profiles for predicted mt proteins in various human tissues, cellular models to study mtPPIs relevant to NDs, and altered mtPPIs in NDs such as Parkinson’s disease (PD), Amyotrophic lateral sclerosis (ALS) and Alzheimer’s disease (AD).Expert opinion: We highlight the scarcity of biomarkers to improve diagnostic accuracy and tracking of ND progression, obstacles in recapitulating NDs using in vitro human cellular models to underpin the pathophysiological mechanisms of the disease, and the shortage of mt protein interactome reference database(s) of neuronal cells in health and disease. These bottlenecks are addressed by discussing improvements in induced pluripotent

PMID: 31987006 [PubMed — as supplied by publisher]
Ataxic Gait in Essential Tremor: A Disease-Associated Feature?

Related Articles

Ataxic Gait in Essential Tremor: A Disease-Associated Feature?

Tremor Other Hyperkinet Mov (N Y). 2019;9:

Authors: Rao AK, Louis ED

Abstract

Background: While accumulating evidence suggests that balance and gait impairments are commonly seen in patients with essential tremor (ET), questions remain regarding their prevalence, their relationship with normal aging, whether they are similar to the impairments seen in spinocerebellar ataxias, their functional consequences, and whether some ET patients carry greater susceptibility.

Methods: We conducted a literature search (until December 2018) on this topic.

Results: We identified 23 articles on gait or balance impairments in ET. The prevalence of balance impairment (missteps on tandem walk test) was seven times higher in ET patients than controls. Gait impairments in ET included reduced speed, increased asymmetry, and impaired dynamic balance. While balance and gait problems worsened with age, ET patients were more impaired than controls, independent of age. The pattern of impairments seen in ET was qualitatively similar to that seen in spinocerebellar ataxias. Balance and gait impairments resulted in greater number of near falls in ET patients. Factors associated with balance and gait impairments in ET included age, presence of tremor in midline structures, and cognitive dysfunction.

Discussion: Accumulating evidence suggests that balance and gait impairments are common in ET patients and occur to a greater extent in controls. Thus, they represent a disease-associated feature. These impairments, which are qualitatively similar to those seen in spinocerebellar ataxias, are not merely subclinical but result in difficulty performing functional tasks and increase falls risk. A subset of patients is more susceptible to balance and gait impairments. The full spectrum of impairments remains to be characterized.

PMID: 31413894 [PubMed — indexed for MEDLINE]

Mapping cis-regulatory chromatin contacts in neural cells links neuropsychiatric disorder risk variants to target genes.

Related Articles

Mapping cis-regulatory chromatin contacts in neural cells links neuropsychiatric disorder risk variants to target genes.

Nat Genet. 2019 08;51(8):1252–1262


Abstract

Mutations in gene regulatory elements have been associated with a wide range of complex neuropsychiatric disorders. However, due to their cell-type specificity and difficulties in characterizing their regulatory targets, the ability to identify causal genetic variants has remained limited. To address these constraints, we perform an integrative analysis of chromatin interactions, open chromatin regions and transcriptomes using promoter capture Hi-C, assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) and RNA sequencing, respectively, in four functionally distinct neural cell types: induced pluripotent stem cell (iPSC)-induced excitatory neurons and lower motor neurons, iPSC-derived hippocampal dentate gyrus-like neurons and primary astrocytes. We identify hundreds of thousands of long-range cis-interactions between promoters and distal promoter-interacting regions, enabling us to link regulatory elements to their target genes and reveal putative processes that are dysregulated in disease. Finally, we validate several promoter-interacting regions by using clustered regularly interspaced short palindromic repeats (CRISPR) techniques in human excitatory neurons, demonstrating that CDK5RAP3, STRAP and DRD2 are transcriptionally regulated by physically linked enhancers.

PMID: 31367015 [PubMed — indexed for MEDLINE]

Codon selection reduces GC content bias in nucleic acids encoding for intrinsically disordered proteins.

Related Articles

Codon selection reduces GC content bias in nucleic acids encoding for intrinsically disordered proteins.


Authors: Oldfield CJ, Peng Z, Uversky VN, Kurgan L

Abstract
Protein-coding nucleic acids exhibit composition and codon biases between sequences coding for intrinsically disordered regions (IDRs) and those coding for structured regions. IDRs are regions of proteins that are folding self-insufficient and which function without the prerequisite of folded structure. Several authors have investigated composition bias or codon selection in regions encoding for IDRs, primarily in Eukaryota, and concluded that elevated GC content is the result of the biased amino acid composition of IDRs. We substantiatively extend previous work by examining GC content in regions encoding IDRs, from 44 species in Eukaryota, Archaea, and Bacteria, spanning a wide range of GC content. We confirm that regions coding for IDRs show a significantly elevated GC content, even across all domains of life. Although this is largely attributable to the amino acid composition bias of IDRs, we show that this bias is independent of the overall GC content and, most importantly, we are the first to observe that GC content bias in IDRs is significantly different than expected from IDR amino acid composition alone. We empirically find compensatory codon selection that reduces the observed GC content bias in IDRs. This selection is dependent on the overall GC content of the organism. The codon selection bias manifests as use of infrequent, AT-rich codons in encoding IDRs. Further, we find these relationships to be independent of the intrinsic disorder prediction method used, and independent of estimated translation efficiency. These observations are consistent with the previous work, and we speculate on whether the observed biases are causal or symptomatic of other driving forces.  

PMID: 31175370 [PubMed — indexed for MEDLINE]

Vortioxetine reverses medial prefrontal cortex-mediated cognitive deficits in male rats induced by castration as a model of androgen deprivation therapy for prostate cancer.

Related Articles  
Vortioxetine reverses medial prefrontal cortex-mediated cognitive deficits in male rats induced by castration as a model of androgen deprivation therapy for prostate cancer.  
Authors: Sharp AM, Lertphinyowong S, Yee SS, Paredes D, Gelfond J, Johnson-Pais TL, Leach RJ, Liss M, Risinger AL, Sullivan AC, Thompson IM, Morilak DA  
Abstract  
RATIONALE: Androgen deprivation therapy (ADT) is an effective treatment for prostate cancer, but induces profound cognitive impairment. Little research has addressed mechanisms underlying these deficits or potential treatments. This is an unmet need to improve quality of life for prostate cancer survivors. OBJECTIVES: We investigated mechanisms of cognitive impairment after ADT in rats and potential utility of the multimodal serotonin-targeting drug, vortioxetine, to improve the impairment, as vortioxetine has specific efficacy against cognitive impairment in depression.  
METHODS: Male Sprague-Dawley rats were surgically castrated. Vortioxetine (28 mg/kg/day) was administered in the diet. The attentional set-shifting test was used to assess medial prefrontal cortex (mPFC) executive function. Afferent-evoked field potentials were recorded in the mPFC of anesthetized rats after stimulating the ventral hippocampus (vHipp) or medial dorsal thalamus (MDT). Gene expression changes were assessed by microarray. Effects of vortioxetine on growth of prostate cancer cells were assessed in vitro.  
RESULTS: ADT impaired cognitive set shifting and attenuated responses evoked in the mPFC by the vHipp afferent, but not the MDT. Both the cognitive impairment and attenuated vHipp-evoked responses were reversed by chronic vortioxetine treatment. Preliminary investigation of gene expression in the mPFC indicates that factors involved in neuronal plasticity and synaptic transmission were down-regulated by castration and up-regulated by vortioxetine in castrated animals. Vortioxetine neither altered the growth of prostate cancer cells in vitro nor interfered with the antiproliferative effects of the androgen antagonist, enzalutamide.  
CONCLUSIONS: These results suggest that vortioxetine may be useful in mitigating cognitive impairment associated with ADT for prostate cancer.  

PMID: 31139875 [PubMed — indexed for MEDLINE]  

In Vivo and In Vitro Monitoring of Amyloid Aggregation via BSA@FGQDs Multimodal Probe.

Related Articles  
In Vivo and In Vitro Monitoring of Amyloid Aggregation via BSA@FGQDs Multimodal Probe.  
Authors: Yousaf M, Ahmad M, Bhatti IA, Nasir A, Hasan M, Jian X, Kalantar-Zadeh K, Mahmood N  
Abstract  
Early detection of peptide aggregate intermediates is quite challenging because of their variable and complex nature as well as due to lack of reliable sensors for diagnosis. Herein, we report the detection of monomers and oligomers using specified fluorescence and a magnetic resonance imaging (MRI) multimodal probe based on bovine-serum-albumin-capped fluorine functionalized graphene quantum dots (BSA@FGQDs). This probe enables in vitro fluorescence-based monitoring of human islet amyloid polypeptide (hIAPP), insulin, and amyloid β(1–42) (Aβ(42)) monomers and oligomers during the fibrillation dynamic. Up to 90% fluorescence quenching of BSA@FGQDs probe upon addition of amyloid monomers/oligomers was observed due to static quenching and nonradiative energy transfer. Moreover, the BSA@FGQDs probe shows 10 times higher signals in detecting amyloid intermediates and fibrils than that of conventional thioflavin dye. A negative Δ G* value (-36.21 kJ/mol) indicates spontaneous interaction of probe with the peptide. These
interactions are hydrogen bonding and hydrophobic as proved by thermodynamic parameters. Visual binding clues of BSA@FGQDs with different morphological states of amyloid protein was achieved through electron microscopy. Furthermore, intravenous and intracranial injection of BSA@FGQDs probe in Alzheimer model mice brain enabled in vivo detection of amyloid plaques in live mice brain by 19F MRI through contrast enhancement. Our proposed probe not only effectively monitors in vitro fibrillation kinetics of number of amyloid proteins with higher sensitivity and specificity than thioflavin dye, but also, the presence of a 19F center makes BSA@FGQDs an effective probe as a noninvasive and nonradiative in vivo detection probe for amyloid plaques.

Hysterectomy Uniquely Impacts Spatial Memory in a Rat Model: A Role for the Nonpregnant Uterus in Cognitive Processes.

Related Articles

Hysterectomy Uniquely Impacts Spatial Memory in a Rat Model: A Role for the Nonpregnant Uterus in Cognitive Processes.

Endocrinology. 2019 01 01;160(1):1–19

Authors: Koebele SV, Palmer JM, Hadder B, Melikian R, Fox C, Strouse IM, DeNardo DF, George C, Daunis E, Nimer A, Mayer LP, Dyer CA, Bimonte-Nelson HA

Abstract

Approximately one-third of women experience hysterectomy, or the surgical removal of the uterus, by 60 years of age, with most surgeries occurring prior to the onset of natural menopause. The ovaries are retained in about half of these surgeries, whereas for the other half hysterectomy occurs concurrently with oophorectomy. The dogma is that the nonpregnant uterus is dormant. There have been no preclinical assessments of surgical variations in menopause, including hysterectomy, with and without ovarian conservation, on potential endocrine and cognitive changes. We present a novel rat model of hysterectomy alongside sham, ovariectomy (Ovx), and Ovx-hysterectomy groups to assess effects of surgical menopause variations. Rats without ovaries learned the working memory domain of a complex cognitive task faster than did those with ovaries. Moreover, uterus removal alone had a unique detrimental impact on the ability to handle a high-demand working memory load. The addition of Ovx, that is, Ovx-hysterectomy, prevented this hysterectomy-induced memory deficit. Performance did not differ amongst groups in reference memory-only tasks, suggesting that the working memory domain is particularly sensitive to variations in surgical menopause.

Following uterus removal, ovarian histology and estrous cycle monitoring demonstrated that ovaries continued to function, and serum assays indicated altered ovarian hormone and gonadotropin profiles by 2 months after surgery. These results underscore the critical need to further study the contribution of the uterus to the female phenotype, including effects of hysterectomy with and without ovarian conservation, on the trajectory of brain and endocrine aging to decipher the impact of common variations in gynecological surgery in women. Moreover, findings demonstrate that the nonpregnant uterus is not dormant, and indicate that there is an ovarian-uterus-brain system that becomes interrupted when the reproductive tract has been disrupted, leading to alterations in brain functioning.

PMID: 30535329 [PubMed — indexed for MEDLINE]