Early cognitive decline after bilateral subthalamic deep brain stimulation in Parkinson’s disease patients with GBA mutations.

Related Articles

Early cognitive decline after bilateral subthalamic deep brain stimulation in Parkinson’s disease patients with GBA mutations.

Parkinsonism Relat Disord. 2020 Jun 09;76:56–62

Abstract

BACKGROUND: Subthalamic nucleus deep brain stimulation (STN-DBS) has demonstrated its efficacy on motor complications in advanced Parkinson’s disease (PD) but does not modify disease progression. Genetic forms of PD have been associated with different cognitive progression profiles.

OBJECTIVE: To assess the effect of PD-related genetic mutations on cognitive outcome after STN-DBS.

METHODS: Patients with STN-DBS were screened for LRRK2, GBA, and PRKN mutations at the Pitié-Salpêtrière Hospital between 1997 and 2009. Patients with known monogenetic forms of PD have been associated with different cognitive progression profiles.

RESULTS: We analyzed 208 patients (131 males, 77 females, 54.3 ± 8.8 years) including 25 GBA, 18 LRRK2, 22 PRKN, and 143 PD patients without mutations. PRKN patients were younger and had a longer disease duration at baseline. A GBA mutation was the only significant genetic factor associated with MDRS change (β = -2.51, p = 0.009). GBA mutation carriers had a more pronounced post-operative MDRS decline (3.2 ± 5.1) than patients with LRRK2 (0.9 ± 4.8), PRKN (0.5 ± 2.7) or controls (1.4 ± 4.4). The motor response to DBS was similar between groups.

CONCLUSION: GBA mutations are associated with early cognitive decline following STN-DBS. Neuropsychological assessment and discussions on the benefit/risk ratio of DBS are particularly important for this population.

PMID: 32866938

Neuronal Selection Based on Relative Fitness Comparison Detects and Eliminates Amyloid-β-Induced Hyperactive Neurons in Drosophila.

Related Articles

Neuronal Selection Based on Relative Fitness Comparison Detects and Eliminates Amyloid-β-Induced Hyperactive Neurons in Drosophila.

iScience. 2020 Aug 18;23(9):101468
Authors: Coelho DS, Moreno E

Abstract

During adult life, damaged but viable neurons can accumulate in the organism, creating increasingly heterogeneous and dysfunctional neural circuits. One intriguing example is the aberrant increased activity of cerebral networks detected in vulnerable brain regions during preclinical stages of Alzheimer’s disease. The pathophysiological contribution of these early functional alterations to the progression of Alzheimer’s disease is uncertain. We found that a unique cell selection mechanism based on relative fitness comparison between neurons is able to target and remove aberrantly active neurons generated by heterologous human amyloid-β in Drosophila. Sustained neuronal activity is sufficient to compromise neuronal fitness and upregulate the expression of the low fitness indicators FlowerLoseB and Azot in the fly. Conversely, forced silencing of neurons restores brain fitness and reduces amyloid-β-induced cell death. The manipulation of this cell selection process, which was already proved to be conserved in humans, might be a promising new avenue to treat Alzheimer’s.

PMID: 32866827
Screening acetylcholinesterase inhibitors from traditional Chinese medicines by paper-immobilized enzyme combined with capillary electrophoresis analysis.

Related Articles

Screening acetylcholinesterase inhibitors from traditional Chinese medicines by paper-immobilized enzyme combined with capillary electrophoresis analysis.

J Pharm Biomed Anal. 2020 Aug 18;190:113547

Authors: Zhao HH, Liu YQ, Chen J

Abstract

Discovering acetylcholinesterase (AChE) inhibitors is one of the important ways to develop new drugs for the treatment of Alzheimer’s disease. In this work, a simple strategy was developed for screening AChE inhibitors from traditional Chinese medicines (TCMs) by capillary electrophoresis (CE) analysis combined with enzymatic assay, in which immobilized AChE was employed. For AChE immobilization, cellulose filter paper (CFP) was used as the carrier material and physically coated with chitosan owing to moderate viscosity of chitosan to be introduced into amino groups, and then AChE was covalently bonded to the amino-functionalized CFP through a Schiff base reaction using glutaraldehyde (GA) as a cross-linking agent. The CFP-immobilized AChE exhibited enhanced endurance to pH and temperature, improved storage stability, excellent repeatability and reusability. More remarkably, CFP-immobilized AChE can be instantly separated from enzyme reaction mixture thus greatly simplifying the operational process. For immobilized AChE, the Michaelis-Menten constant, inhibition constant and IC50 were determined using huperzine A as a model inhibitor. Finally, CFP-immobilized AChE was applied to inhibitor screening from 17 TCMs, among which Chebulae Fructus (ripe fruits of Terminalia chebula) exhibited the strongest inhibitory effect on AChE. The positive results indicated that such a screening strategy may open up a new avenue to discover active components from TCMs.

PMID: 32866617 [PubMed — as supplied by publisher]

Alogliptin reversed hippocampal insulin resistance in an amyloid-beta fibrils induced animal model of Alzheimer’s disease.

Related Articles

Alogliptin reversed hippocampal insulin resistance in an amyloid-beta fibrils induced animal model of Alzheimer’s disease.

Eur J Pharmacol. 2020 Aug 28;173522

Authors: Rahman SO, Kaundal M, Salman M, Shrivastava A, Parvez S, Panda BP, Akhter M, Akhtar M, Najmi AK

Abstract

The complications of Alzheimer’s disease (AD) have made the development of its treatment a challenging task. Several studies have indicated the disruption of insulin receptor substrate-1 (IRS-1) signaling during the development and progression of AD. Surprisingly, the role of a dipeptidyl peptidase-4 (DPP-4) inhibitor on hippocampal IRS-1 signaling has not been investigated before. In this study, we evaluated the efficacy of alogliptin (DPP-4 inhibitor) on hippocampal insulin resistance and associated AD complications. In the present study, amyloid-β (1−42) fibrils were produced and administered intrahippocampally for inducing AD in Wistar rats. After 7 days of surgery, rats were treated with 10 and 20 mg/kg of alogliptin for 28 days. Morris water maze (MWM) test was performed in the last week of our experimental study. Post 24 h of final treatment, rats were euthanized and hippocampi were separated for biochemical and histopathological investigations.
In-silico analysis revealed that alogliptin has a good binding affinity with Aβ and beta-secretase-1 (BACE-1). Alogliptin significantly restored cognitive functions in Aβ (1−42) fibrils injected rats during the MWM test. Alogliptin also significantly attenuated insulin level, IRS-1pS307 expression, Aβ (1−42) level, GSK-3β activity, TNF-α level and oxidative stress in the hippocampus. The histopathological analysis supported alogliptin mediated neuroprotective and anti-amyloidogenic effect. Immunohistochemical analysis also revealed a reduction in IRS-1pS307 expression after alogliptin treatment. The in-silico, behavioral, biochemical and histopathological analysis supports the protective effect of alogliptin against hippocampal insulin resistance and AD.

PMID: 32866503 [PubMed — as supplied by publisher]

Distinct changes in all major components of the neurovascular unit across different neuropathological stages of Alzheimer’s disease.

Related Articles

Distinct changes in all major components of the neurovascular unit across different neuropathological stages of Alzheimer’s disease.

Brain Pathol. 2020 Aug 31.;

Authors: Kirabali T, Rust R, Rigotti S, Siccoli A, Nitsch RM, Kulić L

Abstract
In the brain capillaries, endothelial cells, pericytes, astrocytes, and microglia form a structural and functional complex called neurovascular unit (NVU) which is critically involved in maintaining neuronal homeostasis. In the present study, we applied a comprehensive immunohistochemical approach to investigate the structural alterations in the NVU across different Alzheimer’s disease (AD) neuropathological stages. Post-mortem human cortical and hippocampal samples derived from AD patients and non-demented elderly control individuals were immunostained using a panel of markers representing specific components of the NVU including Collagen IV (basement membrane), PDGFR-β (pericytes), GFAP (astrocytes), Iba1 (microglia), MRC1 (perivascular macrophages) and lectin as an endothelial cell label. Astrocytes (GFAP) and microglia (Iba1) were quantified both in the whole visual-field and specifically within the NVU, and the sample set was additionally analyzed using anti-tau (AT8) and three different anti-Aβ (clones G2-10, G2-11, 4G8) antibodies. Analyses of lectin labeled sections showed an altered vascular distribution in AD patients as revealed by a reduced nearest distance between capillaries. Within the NVU, a Braak-stage dependent reduction in pericyte coverage was identified as the earliest structural alteration during AD progression. In comparison to non-demented elderly controls, AD patients showed a significantly higher astrocyte coverage within the NVU, which was paralleled by a reduced microglial coverage around capillaries. Assessment of perivascular macrophages moreover demonstrated a relocation of these cells from leptomeningeal arteries to penetrating parenchymal vessels in AD patients. Collectively, the results of our study represent a comprehensive first in-depth analysis of AD-related structural changes of the NVU and suggest distinct alterations in all components of the NVU during AD progression.

PMID: 32866303 [PubMed — as supplied by publisher]

Spectral dynamic causal modelling of resting-state fMRI: an exploratory study relating effective brain connectivity in the default mode network to genetics.

Related Articles

Spectral dynamic causal modelling of resting-state fMRI: an exploratory study relating effective brain connectivity in the default mode network to genetics.


Abstract
We conduct an imaging genetics study to explore how effective brain connectivity in the default mode network (DMN) may be related to genetics within the context of Alzheimer’s disease and mild cognitive impairment. We develop an analysis of longitudinal resting-state functional magnetic resonance imaging (rs-fMRI) and genetic data obtained from a sample of 111 subjects with a total of 319 rs-fMRI scans from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database. A Dynamic Causal Model (DCM) is fit to the rs-fMRI scans to estimate effective brain connectivity within the DMN and related to a set of single nucleotide polymorphisms (SNPs) contained in an empirical disease-constrained set which is obtained out-of-sample from 663 ADNI subjects having only genome-wide data. We relate longitudinal effective brain connectivity estimated using spectral DCM to SNPs using both linear mixed effect (LME) models as well as function-on-scalar regression (FSR). In both cases we implement a parametric bootstrap for testing SNP coefficients and make comparisons with p-values obtained from asymptotic null distributions. In both networks at an initial q-value threshold of 0.1 no effects are found. We report on exploratory patterns of associations with relatively high ranks that exhibit stability to the differing assumptions made by both FSR and LME.

PMID: 32866136 [PubMed — as supplied by publisher]
Cross Talk between Mitochondria and Other Targets in Alzheimer’s Disease.

Related Articles
Cross Talk between Mitochondria and Other Targets in Alzheimer’s Disease.
Authors: Khatoon R, Pahuja M, Parvez S

Abstract
Among the neurodegenerative diseases, Alzheimer’s disease (AD) is a predominant public health issue, affecting 16 million people around the world. It is clinically manifested by the presence of amyloid plaques (Aβ) and neurofibrillary tangles (NFT) within the brain. Due to intraneuronal processing, Aβ interacts with cellular targets such as mitochondria, ER, and Golgi apparatus and hampers their normal functions. Alteration in the mitochondrial function, closely related to the production of reactive oxygen species (ROS), Ca++ overload, and apoptosis in the brain, is one of the key pathological events studied in AD pathogenesis. It is also an important pivot for the intracellular interaction with ER and Golgi through signal transduction and membrane contact to regulate cell survival and death mechanism. Alteration in mitochondrial function is intimately connected with abnormal ER or Golgi function. Stimuli that enhance perturbation in the normal ER or Golgi organelles function can involve mitochondria mediated apoptotic cell death. In this review, we address the importance of the mitochondria and their cross talk with ER and Golgi in AD pathogenesis and animal models with a therapeutic strategy to improve the mitochondrial functions.

PMID: 32865917 [PubMed — as supplied by publisher]

High Blood Lead Levels: An Increased Risk for Development of Brain Hyperintensities among Type 2 Diabetes Mellitus Patients.

Related Articles
High Blood Lead Levels: An Increased Risk for Development of Brain Hyperintensities among Type 2 Diabetes Mellitus Patients.
Biol Trace Elem Res. 2020 Aug 31;:
Authors: Al-Anbari HSN, Ismail DK, Hasan MK, Aga QAAK, Shinu P, Nair AB

Abstract
The current study was aimed to ascertain the effect of blood lead level on brain tissues in patients with type 2 diabetes. A total of 300 human participants ages 27 to 60 years with type 2 diabetes (n = 150) and healthy individuals (n = 150) were included in this study. The serum samples were used for measuring HbA1c and fasting blood glucose. Blood lead level was measured using flame atomic absorption spectrophotometer. Magnetic resonance imaging sub-analysis was used to assess the brain hyperintensities. Brain hyperintensities were found in 55% of patients with diabetes and 6% of non-diabetic control group subjects. The deep white matter hyperintensities were observed in 45% of diabetic patients, while the subcortical hyperintensities were noted in 10% of cases. Entorhinal cortex changes (31%) and hippocampus changes (42%) were noted in diabetic patients with brain hyperintensities. Diabetic patients with brain hyperintensities showed higher blood lead levels, HbA1c, and fasting blood sugar (p
PMID: 32865724 [PubMed — as supplied by publisher]

Cerebral blood flow decrease as an early pathological mechanism in Alzheimer’s disease.

Related Articles
Cerebral blood flow decrease as an early pathological mechanism in Alzheimer’s disease.
Acta Neuropathol. 2020 Aug 31;:
Authors: Korte N, Nortley R, Attwell D

Abstract
Therapies targeting late events in Alzheimer’s disease (AD), including aggregation of amyloid beta (Aβ) and hyperphosphorylated tau, have largely failed, probably because they are given after significant neuronal damage has occurred. Biomarkers suggest that the earliest event in AD is a decrease of cerebral blood flow (CBF). This is caused by constriction of capillaries by contractile pericytes, probably evoked by oligomeric Aβ. CBF is also reduced by neutrophil trapping in capillaries and clot formation, perhaps secondary to the capillary constriction. The fall in CBF potentiates neurodegeneration by upregulating the BACE1 enzyme that makes Aβ and by promoting tau hyperphosphorylation. Surprisingly, therefore, CBF reduction may play a crucial role in driving cognitive decline by initiating the amyloid cascade itself, or being caused by and amplifying Aβ production. Here, we review developments in this area that are neglected in current approaches to AD, with the aim of promoting novel mechanism-based therapeutic approaches.

PMID: 32865691 [PubMed — as supplied by publisher]
Antioxidant Modulation of mTOR and Sirtuin Pathways in Age-Related Neurodegenerative Diseases.

 Related Articles

Antioxidant Modulation of mTOR and Sirtuin Pathways in Age-Related Neurodegenerative Diseases.

Mol Neurobiol. 2020 Aug 31;:

Authors: Abdullah A, Mohd Murshid N, Makpol S

Abstract

In the human body, cell division and metabolism are expected to transpire uneventfully for approximately 25 years. Then, secondary metabolism and cell damage products accumulate, and ageing phenotypes are acquired, causing the progression of disease. Among these age-related diseases, neurodegenerative diseases have attracted considerable attention because of their irreversibility, the absence of effective treatment and their relationship with social and economic pressures. Mechanistic (formerly mammalian) target of rapamycin (mTOR), sirtuin (SIRT) and insulin/insulin growth factor 1 (IGF1) signalling pathways are among the most important pathways in ageing-associated conditions, such as neurodegeneration. These longevity-related pathways are associated with a diversity of various processes, including metabolism, cognition, stress reaction and brain plasticity. In this review, we discuss the roles of sirtuin and mTOR in ageing and neurodegeneration, with an emphasis on their regulation of autophagy, apoptosis and mitochondrial energy metabolism. The intervention of neurodegeneration using potential antioxidants, including vitamins, phytochemicals, resveratrol, herbs, curcumin, coenzyme Q10 and minerals, specifically aimed at retaining mitochondrial function in the treatment of Alzheimer’s disease, Parkinson’s disease and Huntington’s disease is highlighted.

PMID: 32865663 [PubMed — as supplied by publisher]

Type of Androgen Deprivation Therapy and Risk of Dementia Among Patients With Prostate Cancer in Taiwan.

 Related Articles

Type of Androgen Deprivation Therapy and Risk of Dementia Among Patients With Prostate Cancer in Taiwan.

JAMA Netw Open. 2020 Aug 03;3(8):e2015189

Authors: Huang WK, Liu CH, Pang ST, Liu JR, Chang JW, Liaw CC, Hsu CL, Lin YC, See LC

Abstract

Importance: It remains unclear whether androgen deprivation therapy (ADT) is associated with subsequent dementia risk in patients with prostate cancer. There are limited data regarding dementia risk across ADT types.

Objective: To examine the association between all-cause dementia, including Alzheimer disease (AD), and different ADT types in patients with prostate cancer.

Design, Setting, and Participants: This cohort study used linked data from the Taiwan National Cancer Registry, the National Health Insurance Research Database, and the Taiwan National Death Registry. A cohort of 23,651 patients with newly diagnosed prostate cancer between January 1, 2008, and December 31, 2015, was identified and followed up from 1 year after diagnosis until December 31, 2017. Data analysis was performed between January 2019 and May 2020.

Exposures: Patients who received and did not receive ADT, including gonadotropin-releasing hormone (GnRH) agonists, orchiectomy, or antiandrogen monotherapy.

Main Outcomes and Measures: The primary outcomes were all-cause dementia or AD. Stabilized inverse probability of treatment weighting was used to balance baseline covariates. The association between dementia and various ADT types was examined using the Cox proportional hazards model. Furthermore, a multivariate Cox proportional model with age as the time scale was conducted for complementary comparison.

Results: In the cohort of 23,651 male patients (median [interquartile range] age, 73 [66–79] years), 6904 (29.2%) did not receive ADT, 11,817 (50.0%) received GnRH agonists, 876 (3.7%) received orchiectomy, and 4054 (17.1%) received antiandrogen monotherapy. Overall, 1525 patients were diagnosed with incident dementia (1.72 per 100 person-years) during a median (interquartile range) follow-up of 3.46 (1.92–5.51) years. Compared with those who did not receive ADT, those using antiandrogen monotherapy showed an increased risk of dementia (weighted hazard ratio [HR], 1.34; 95% CI, 1.16–1.55) and AD (weighted HR, 1.52; 95% CI, 1.13–2.04). The risk of dementia was similar between GnRH agonist use or orchiectomy and no ADT use (GnRH agonist: weighted HR, 1.13; 95% CI, 1.00–1.28; orchiectomy: 1.00; 95% CI, 0.74–1.37). Several sensitivity analyses revealed consistent findings for both outcomes.

Conclusions and Relevance: In this study, the use of antiandrogen monotherapy was associated with increased risk of dementia or AD, while GnRH agonist use and orchiectomy had no significant difference compared with patients who did not receive ADT. Further prospective studies are warranted to confirm these findings.

PMID: 32865575 [PubMed — as supplied by publisher]
Mentorship and Training to Increase Diversity of Researchers and Practitioners in the Field of Aging and Alzheimer’s Disease: A Scoping Review of Program Characteristics.

Related Articles

Mentorship and Training to Increase Diversity of Researchers and Practitioners in the Field of Aging and Alzheimer’s Disease: A Scoping Review of Program Characteristics.

J Aging Health. 2020 Aug 31;:898264320953345

Authors: Ureña S, Ingram LA, Leith K, Lohman MC, Resciniti N, Rubin L, Miller MC, Friedman DB

Abstract

Objectives: Diversity is needed within the aging and Alzheimer’s disease and related dementias (ADRD) research and practice workforce to comprehensively address health inequities faced by underrepresented minority (URM) older adults. We conducted a scoping review of training programs designed to diversify the pool of researchers and practitioners in the field of aging and ADRD.

Methods: Online database searches yielded 3976 articles published from 1999 to 2019. Fourteen studies met the inclusion criteria. Results: All programs were from the United States and included URM populations. Nine programs included students, one targeted university faculty, and four targeted clinical staff. Only five programs were guided by theory. Discussion: Our review identified URMs’ desire for culturally diverse and representative mentorship, the need for career development support at various training stages, and the importance of incorporating theory to program design. It also identified key characteristics for future program development, creation of systematic evaluation standards, and opportunities for promotion.

PMID: 32865457 [PubMed — as supplied by publisher]


Related Articles


EMBO J. 2020 Aug 31;:e103791


Abstract

The link between cholesterol homeostasis and cleavage of the amyloid precursor protein (APP), and how this relationship relates to Alzheimer’s disease (AD) pathogenesis, is still unknown. Cellular cholesterol levels are regulated through crosstalk between the plasma membrane (PM), where most cellular cholesterol resides, and the endoplasmic reticulum (ER), where the protein machinery that regulates cholesterol levels resides. The intracellular transport of cholesterol from the PM to the ER is believed to be activated by a lipid-sensing peptid(e)(s) in the ER that can cluster PM-derived cholesterol into transient detergent-resistant membrane domains (DRMs) within the ER, also called the ER regulatory pool of cholesterol. When formed, these cholesterol-rich domains in the ER maintain cellular homeostasis by inducing cholesterol esterification as a mechanism of detoxification while attenuating its de novo synthesis. In this manuscript, we propose that the 99-aa C-terminal fragment of APP (C99), when delivered to the ER for cleavage by γ-secretase, acts as a lipid-sensing peptide that forms regulatory DRMs in the ER, called mitochondria-associated ER membranes (MAM). Our data in cellular AD models indicates that increased levels of uncleaved C99 in the ER, an early phenotype of the disease, upregulates the formation of these transient DRMs by inducing the internalization of extracellular cholesterol and its trafficking from the PM to the ER. These results suggest a novel role for C99 as a mediator of cholesterol disturbances in AD, potentially explaining early hallmarks of the disease.

PMID: 32865299 [PubMed — as supplied by publisher]

Attenuation of the extracellular matrix restores microglial activity during the early stage of amyloidosis.

Related Articles

Attenuation of the extracellular matrix restores microglial activity during the early stage of amyloidosis.

Glia. 2020 Aug 31;:

Authors: Stoyanov S, Sun W, Düsedau HP, Cangalaya C, Choi I, Mirzapourdelavar H, Baidoe-Ansah D, Kaushik R, Neumann J, Dunay IR, Dityatev A

Abstract

In the advanced stages of Alzheimer’s disease (AD), microglia are transformed to an activated phenotype with thickened and retracted processes, migrate to the site of amyloid-beta (Aβ) plaques, and proliferate. In the early stages of AD, it is still poorly understood whether the microglial function is altered and which factors may regulate these changes. Here, we focused on studying microglia in the retrosplenial cortex (RSC) in 3- to 4-month-old 5xFAD mice as a transgenic mouse model of AD. At this age, there are neither Aβ plaques, nor activation of microglia, nor dysregulation in the expression of genes encoding major extracellular matrix (ECM) molecules or extracellular proteases in
the RSC. Still, histochemical evaluation of the fine structure of neural ECM revealed increased levels of Wisteria floribunda agglutinin labeling in holes of perineuronal nets and changes in the perimeter of ECM barriers around the holes in 5xFAD mice. Two-photon vital microscopy demonstrated normal morphology and resting motility of microglia but strongly diminished number of microglial cells that migrated to the photosesion site in 5xFAD mice. Enzymatic digestion of ECM by chondroitinase ABC (ChABC) ameliorated this defect. Accordingly, the characterization of cell surface markers by flow cytometry demonstrated altered expression of microglial CD45. Moreover, ChABC treatment reduced the invasion of myeloid-derived mononuclear cells into the RSC of 5xFAD mice. Hence, the migration of both microglia and myeloid cells is altered during the early stages of amyloidosis and can be restored at least partially by the attenuation of the ECM.

PMID: 32865286 [PubMed — as supplied by publisher]

Neighborhood-Level Social Disadvantage and Risk of Delirium Following Major Surgery.

Related Articles

Selective linkage of mitochondrial enzymes to intracellular calcium stores differs between human induced pluripotent stem cells, neural stem cells and neurons.

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Selective linkage of mitochondrial enzymes to intracellular calcium stores differs between human induced pluripotent stem cells, neural stem cells and neurons.

PMID: 32865254 [PubMed — as supplied by publisher]
**human neurons verify a link between KGDHC and releasable ER calcium stores, and support the use of human neurons to examine mechanisms and potential therapies for AD.**

PMID: 32865230 [PubMed — as supplied by publisher]

**Associations Between Alzheimer’s Disease and Related Dementias and Depressive Symptoms of Partner Caregivers.**

Related Articles

**Associations Between Alzheimer’s Disease and Related Dementias and Depressive Symptoms of Partner Caregivers.**

J Appl Gerontol. 2020 Aug 29;.733464820952252

Authors: Harris ML, Titler MG, Hoffman GJ

Abstract

Family members—mainly spouses and partners—are the primary caregivers for individuals with Alzheimer’s disease and related dementias (ADRDs), chronic progressive illnesses requiring increasing levels of care. We performed a retrospective observational analysis comparing depressive symptoms of 16,650 older individuals with partners without ADRDs, and those recently (within 2 years) or less recently diagnosed (≥2 years prior), controlling for lagged sociodemographic and health characteristics. The mean number of reported depressive symptoms was 1.2 (SD = 1.8). Compared with respondents with partners with no ADRD, having a partner with any ADRD was associated with a 0.35 increase (95% confidence interval [CI] = [0.30, 0.41]), or 30% increase, in depressive symptoms. A less recent partner diagnosis was associated with a 33% increase, while a recent diagnosis was associated with a 27% increase. Clinically meaningful and longitudinally worsening depressive symptoms amplify the need to prioritize partner health and family-centered care following an ADRD diagnosis.

PMID: 32864956 [PubMed — as supplied by publisher]

**Observation of the elevation of cholinesterases activity in brain glioma by a near-infrared emission chemsensor.**

Related Articles

**Observation of the elevation of cholinesterases activity in brain glioma by a near-infrared emission chemsensor.**

Anal Chem. 2020 Aug 31:;

Authors: Ma Y, Gao W, Ma S, Liu Y, Lin W

Abstract

The excessive expression of cholinesterases (ChEs) directly disturbs the metabolism of acetylcholine (ACh), causing disordering neurotransmission in the brain or even Alzheimer’s disease and cancer. However, the variation of ChEs including cetylcholinesterase and butyrylcholinesterase in brain glioma has not yet been investigated. Therefore, the development of a suitable method for in situ imaging ChEs in brain tissue to understand the physiological functions of ChEs in depth is very important. Herein, a new near-infrared emission fluorescent probe (IPAN) for visualization of ChEs activity was developed. IPAN exhibits ultrafast response to ChEs, low detection limit for AChE (0.127 U/mL) and BChE (0.0117 U/mL) as well as a large Stokes shift with near-infrared emission. Based on these excellent attributes, the IPAN was effectively utilized for in-aging the fluctuations of ChEs activity in the apoptosis cells and zebrafish. Notably, by utilizing the unique probe IPAN, we observed a significant enhancement of ChEs activity in the tumor cells and brain glioma, for the first time. We believe that this interesting finding could provide a powerful guidance for tumor resection in the future.

PMID: 32864956 [PubMed — as supplied by publisher]

**Mechanistic insights into chromatin targeting by leukemic NUP98-PHF23 fusion.**

Related Articles

**Mechanistic insights into chromatin targeting by leukemic NUP98-PHF23 fusion.**

Nat Commun. 2020 07 03;11(1):3339


Abstract

Chromosomal NUP98-PHF23 translocation is associated with an aggressive form of acute myeloid leukemia (AML) and poor survival rate. Here, we report the molecular mechanisms by which NUP98-PHF23 recognizes the histone mark H3K4me3 and is inhibited by small molecule compounds, including disulfiram that directly targets the PHD finger of PHF23 (PHF23PHD). Our data support a critical role for the PHD fingers of NUP98-PHF23, and related NUP98-KDM5A and NUP98-BPTF fusions in driving leukemogenesis, and demonstrate that blocking this interaction in NUP98-PHF23 expressing AML cells leads to cell death through necrotic and late apoptosis pathways. An overlap of NUP98-KDM5A oncoprotein binding sites and H3K4me3-positive loci at the Hoxa/b gene clusters and Meis1 in ChIP-seq, together with NMR analysis of the H3K4me3-binding sites of the PHD fingers from PHF23, KDM5A and BPTF, suggests a common PHD finger-dependent mechanism that promotes leukemogenesis by this type of NUP98 fusions. Our findings highlight the direct correlation between the abilities of NUP98-PHD finger fusion chimeras to associate with H3K4me3-enriched chromatin and leukemic transformation.

PMID: 32620764 [PubMed — indexed for MEDLINE]
Prolonged tau clearance and stress vulnerability rescue by pharmacological activation of autophagy in tauopathy neurons.

Related Articles

**Prolonged tau clearance and stress vulnerability rescue by pharmacological activation of autophagy in tauopathy neurons.**

Nat Commun. 2020 06 26;11(1):3258


Abstract

Tauopathies are neurodegenerative diseases associated with accumulation of abnormal tau protein in the brain. Patient iPSC-derived neuronal cell models replicate disease-relevant phenotypes ex vivo that can be pharmacologically targeted for drug discovery. Here, we explored autophagy as a mechanism to reduce tau burden in human neurons and, from a small-molecule screen, identify the mTOR inhibitors OSI-027, AZD2014 and AZD8055. These compounds are more potent than rapamycin, and robustly downregulate phosphorylated and insoluble tau, consequently reducing tau-mediated neuronal stress vulnerability. MTORC1 inhibition and autophagy activity are directly linked to tau clearance. Notably, single-dose treatment followed by washout leads to a prolonged reduction of tau levels and toxicity for 12 days, which is mirrored by a sustained effect on MTORC1 inhibition and autophagy. This new insight into the pharmacodynamics of mTOR inhibitors in regulation of neuronal autophagy may contribute to development of therapies for tauopathies.

PMID: 32591533 [PubMed — indexed for MEDLINE]

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Apolipoprotein ε4 allele is associated with frailty syndrome: results from the hellenic longitudinal investigation of ageing and diet study.

Related Articles

**Apolipoprotein ε4 allele is associated with frailty syndrome: results from the hellenic longitudinal investigation of ageing and diet study.**

Age Ageing. 2019 11 01;48(6):917–921

Authors: Mourtzi N, Ntanasi E, Yannakoulia M, Kosmidis M, Anastasiou C, Dardiotis E, Hadjigeorgiou G, Sakka P, Scarmeas N

Abstract

Apolipoprotein (APOE) ε4 allele has been associated with a number of age-related diseases but previous studies failed to identify any link with Frailty syndrome. The aim of the present study is to investigate the association between APOE ε4 allele and frailty syndrome. We operationalised Frailty according to the Fried definition, and we determined the APOE genotype in 1234 participants of the hellenic longitudinal investigation of ageing and diet study. Logistic regression analyses were performed to examine the association between APOE ε4 allele and frailty. Models were adjusted for age, education, sex, presence (or absence) of hypertension, diabetes, myocardial infarction, coronary disease, congestive heart failure, arrhythmia or other heart disease, family history of dementia and current smoking. The same models were performed after exclusion of patients with dementia and participants with APOE ε2/ε4 genotype. In the fully adjusted model, carriers of APOE ε4 allele had 2.753 higher odds of frailty relative to non-carriers. After trichotomization of APOE genotype, APOE ε4 heterozygotes had 2.675 higher risk of frailty compared to non-carriers while exclusion of patients with dementia or/and APOE ε2/ε4 genotype did not alter the

PMID: 31558366 [PubMed — indexed for MEDLINE]

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Multidomain intervention and/or omega-3 in nondemented elderly subjects according to amyloid status.

Related Articles

**Multidomain intervention and/or omega-3 in nondemented elderly subjects according to amyloid status.**


Authors: Delrieu J, Payoux P, Carrié I, Cantet C, Weiner M, Vellas B, Andrieu S

Abstract

INTRODUCTION: The Multidomain Alzheimer Preventive Trial (MAPT) assessed the efficacy of omega-3 fatty acid supplementation, a multidomain intervention (MI), or a combination of both on cognition. Impact according to cerebral amyloid status was evaluated by PET scan.

METHODS: Participants were nondemented and had memory complaints, limitation in one instrumental activity of daily living, or slow gait. The primary outcome was a change from baseline in 36 months measured with a cognitive composite Z score.

RESULTS: No effect was observed on cognition in the negative amyloid group (n = 167). In the positive amyloid group (n = 102), we observed a difference of 0.708 and 0.471 in the cognitive composite score between the MI plus omega-3 fatty acid group, the MI alone group, and the placebo group, respectively.

DISCUSSION: MI alone or in combination with omega-3 fatty acids was associated with improved primary cognitive outcome in subjects with positive amyloid status.

TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01513252.

PMID: 32591533 [PubMed — indexed for MEDLINE]
association. The APOE ε4 allele may be a significant biomarker of frailty with diagnostic and prognostic capacity.

PMID: 31504089 [PubMed — indexed for MEDLINE]

Chirality-Selected Chemical Modulation of Amyloid Aggregation.

Related Articles

Chirality-Selected Chemical Modulation of Amyloid Aggregation.

J Am Chem Soc. 2019 05 01;141(17):6915–6921

Authors: Gao N, Du Z, Guan Y, Dong K, Ren J, Qu X

Abstract

Due to the composed α-helical/β-strand structures, β-amyloid peptide (Aβ) is sensitive to chiral environments. The orientation and chirality of the Aβ strand strongly influence its aggregation. Aβ-formed fibrils have a cascade of chirality. Therefore, for selectively targeting amyloid aggregates, chirality preference can be one key issue. Inspired by the natural stereoselectivity and the β-sheet structure, herein, we synthesized a series of d- and l-amino acid-modified polyoxometalate (POM) derivatives, including positively charged amino acids (d-His and l-His) and negatively charged (d-Glu and l-Glu) and hydrophobic amino acids (d-Leu, l-Leu, d-Phe, and l-Phe), to modulate Aβ aggregation. Intriguingly, Phe-modified POMs showed a stronger inhibition effect than other amino acid-modified POMs, as evidenced by multiple biophysical and spectral assays, including fluorescence, circular dichroism, NMR, molecular dynamic simulations, and isothermal titration calorimetry. More importantly, d-Phe-modified POM had an 8-fold stronger inhibition effect than l-Phe-modified POM, indicating high enantioselectivity. Furthermore, in vivo studies demonstrated that the chiral POM derivatives crossed the blood-brain barrier, extended the life span of AD transgenic Caenorhabditis elegans CL2006 strain, and had low cytotoxicity, even at a high dosage.

PMID: 30969760 [PubMed — indexed for MEDLINE]