IN BRIEF

ALZHEIMER DISEASE

Exercise wards off Alzheimer disease by boosting neurogenesis and neuroprotective factors

Exercise might protect against Alzheimer disease (AD) by promoting neurogenesis and raising the levels of brain-derived neurotrophic factor (BDNF), according to a new study. Previous work has suggested that exercise reduces the risk of AD, but the mechanism underlying this association is unclear. In the new study, Choi et al. found that exercise boosted hippocampal neurogenesis, reduced amyloid-β levels, increased the levels of BDNF and improved memory in a mouse model of AD. Ablation of neurogenesis prevented the beneficial effects of exercise in this model. However, genetic or pharmacological induction of neurogenesis in the absence of exercise failed to improve memory. Only the combination of neurogenesis induction with overexpression of BDNF mimicked the memory improvements elicited by exercise. The results suggest that boosting neurogenesis might protect against AD, but only when the health of the local brain environment is also improved.

ORIGINAL ARTICLE Choi, S. H. et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science* **361**, eaan8821 (2018)

NEURODEGENERATIVE DISEASE

Nodding syndrome discovered to be a tauopathy

Nodding syndrome is a neurological condition of unknown cause that affects children in East Africa. The condition is characterized by cognitive impairment, stunted growth, seizures and stereotypical nodding of the head, and can lead to progressive neurological deterioration and death. Now, a new immunohistochemistry study has identified tau neuronal neurofibrillary tangles, neuropil threads and dot-like lesions in post-mortem brains of individuals with nodding syndrome. The pathology was found to preferentially affect the frontal and temporal lobes, most prominently on the crests of gyri. The findings shed new light on the underlying mechanisms of this understudied epidemic disorder and open new potential lines of enquiry into the elusive cause of the disease.

ORIGINAL ARTICLE Pollanen, M. S. et al. Nodding syndrome in Uganda is a tauopathy. *Acta Neuropathol.* https://doi.org/10.1007/s00401-018-1909-9 (2018)

NEURO-ONCOLOGY

BRAF mutation promotes epilepsy in paediatric brain tumours

The *BRAF* p.Val600Glu mutation (*BRAF*^{V600E}) promotes epileptogenic properties in neuronal cells in paediatric brain tumours, new research has shown. Treatment-refractory seizures are a common symptom of paediatric brain tumours, but the causes of this epilepsy are unknown. In the new study, researchers developed a mouse model that expressed the *Braf*^{V600E} mutation in early brain development. The mutation elicited tumorigenic properties in glial cells but epileptogenic properties in neuronal cells. Analysis of brain samples from patients with the mutation revealed increased levels of REST, an epilepsy-associated transcription factor. Interestingly, the team also found that they could alleviate seizures in their mouse model via treatment with the BRAF^{V600E} inhibitor vemurafenib or via genetic inhibition of *Rest*. These results suggest that BRAF and REST are potential targets for new treatments of epilepsy in paediatric brain tumours.

ORIGINAL ARTICLE Koh, H. Y. et al. BRAF somatic mutation contributes to intrinsic epileptogenicity in pediatric brain tumors. *Nat. Med.* https://doi.org/10.1038/s41591-018-0172-x (2018)

NEURODEGENERATIVE DISEASE

Huntington disease — a neurodevelopmental disorder?

Certain prodromal features of Huntington disease (HD) manifest in early life and could be amenable to therapeutic intervention at this stage, new research indicates. During the early postnatal period in rodent models of HD, animals showed characteristic molecular, cellular and behavioural changes that could be reversed by treatment with a histone deacetylase inhibitor (HDACi).

"In 2003, we reported on the generation and characterization of the first transgenic rat model of HD," explains study leader Stephan von Hörsten. "Subsequently, to our surprise, we found that behavioural abnormalities preceded the onset of overt huntingtin protein aggregation in this model, and this finding prompted us to look further into the perinatal period."

HD is caused by CAG repeat expansions in exon 1 of the huntingtin gene (*HTT*). Expression of these repeats results in production of an aggregation-prone and potentially neurotoxic form of the huntingtin protein.

For the new study, von Hörsten and colleagues used tgHD rats and BACHD mice, which express mutant *HTT* transgenes with 51 and 97 CAG repeats, respectively. BACHD mice develop an HD-like phenotype during early adulthood; the disease manifests slightly later in tgHD rats.

In the early postnatal period, both models showed a behavioural phenotype, which included a reduction in ultrasonic vocalization and an increase in risk-taking behaviour. Analysis of striatal gene expression in tgHD rats uncovered evidence of dopaminergic imbalance. In addition, neural stem cells from tgHD pups and BACHD embryos showed an impaired ability to differentiate into neurons and oligodendrocytes.

NEUROMUSCULAR DISEASE

CRISPR therapy shows promise in Duchenne muscular dystrophy

A gene-editing therapy for Duchenne muscular dystrophy (DMD) restores expression of dystrophin in a canine model of the disease, a new study has shown. The findings provide the first indication that gene editing is a feasible strategy for treatment of DMD in large mammals, and suggests that this therapy has promise for future clinical trials.

DMD is a genetic disorder that leads to progressive muscle degeneration and premature death owing to respiratory failure and cardiomyopathy. The disease results from mutations in *DMD*, the gene that encodes dystrophin. Many of these mutations cause a frameshift that leads to near-complete loss of this protein. An antisense oligonucleotide therapy was controversially approved for DMD in 2016, despite yielding <1% increases in dystrophin levels, with questionable benefits to patients.

In the new study, Eric Olson and colleagues tested a CRISPR–Cas9 gene-editing therapy in a dog model of DMD. The team injected four dogs with adeno-associated virus 9 carrying CRISPR–Cas9 components targeted to dystrophin.

The therapy successfully restored the normal reading frame of *DMD* in the injected animals. Levels of dystrophin were substantially increased across a range of muscles in the dogs at 6 weeks after intramuscular delivery or 8 weeks after systemic delivery of the treatment. Between 3% and 90% of the normal healthy levels of dystrophin were observed, depending on the muscle. Dystrophin levels reached 92% of normal in the cardiac muscle of the dog that received the highest treatment dose.