Restoration of olfactory neural circuitry following disruption.

https://neurodegenerationresearch.eu/survey/restoration-of-olfactory-neural-circuitry-following-disruption/

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USA

Title of project or programme

Restoration of olfactory neural circuitry following disruption.

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NIH (NIA)

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Start date of award
Total duration of award in years

7

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Injury (total) Accidents/Adverse Effects... Injury - Trauma - (Head and Spine)... Injury - Traumatic brain injury... Neurodegenerative... Neurosciences... Regenerative Medicine

Research Abstract

The olfactory system is ideally suited for studies of neural circuit disruption and repair. Primary olfactory sensory neurons (OSNs) contain a unique set of molecular markers in the odorant

receptors (ORs) that they express which are both diverse and specific. In addition, the precise order that is generated by OSN projections to the olfactory bulb (0B) and subsequently within the OB network itself, provides a precise framework from which to judge network alterations. One method that we have been using to cause olfactory circuit disruption is to induce neurodegeneration through the expression of a humanized mutant form of the Amyloid Precursor Protein (APP) in mature OSNs. Since APP expression is associated with Alzheimers disease (AD) and olfactory loss is common among AD patients we used this approach to establish a mouse model for studying the underlying mechanisms. The regenerative capacity of the olfactory system made this model particularly useful as we could also evaluate the systems ability to recover following the neurodegenerative-induced disruption. Previously, we showed using this model that APP overexpression causes clear cell-autonomous apoptosis of OSNs and loss of axonal projections to the olfactory bulb (OB) but that the system can be restored if APP expression is suppressed. Although, it was unclear if any of these APP-induced anatomical changes could be detected through noninvasive measures. This past year we sought to determine if Magnetic Resonance Imaging (MRI) could be used to detect the APP induced disruption and recovery of OSNs. To approach this, we used Manganese Enhanced MRI (MEMRI) which we had previously used to achieve very high resolution imaging of the mouse OB. Together with our animal model we were able to successfully demonstrate that MEMRI could indeed be used to detect both the loss of OSN axons in the OB as well as the restoration of projections following shutdown of APP expression by measuring changes in the OB laminar structure (Saar et al, 2015). We suggest that this approach could potentially provide a non-invasive means for detecting neurodegenerative induced loss in the olfactory system of AD patients. To determine the underlying mechanism of APP induced apoptosis within OSNs we examined the potential role of amyloid beta (Abeta) peptides. Using multiple mouse models, we tested the ability of APP overexpression to cause cell death in the absence of Abeta and found that Abeta was not required for APP induced apoptosis of OSNs. In addition, we revealed a clear cell-autonomous mechanism involving the intrinsic apoptosis pathway linked to mitochondrial dysfunction and potentially cell stress (Cheng et al., 2016). In a collaborative study we also evaluated olfactory impairment associated with traumatic brain injury (TBI) linked to blast injured troops. Using quantitative olfactory measures designed to evaluate odor identification we found high specificity as a marker for detecting structural neuropathology associated with head trauma (Xydakis et al., 2015). Thus, we believe olfactory measures could be useful to help diagnose TBI and possibly also to help track the progression or recovery from the disruption. Together, these studies emphasize the sensitivity of the olfactory system and its ability to regenerate which makes it a very useful platform to study neural disruption and repair.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A