both the NHANES and CSHA studies. Furthermore, our method is shown to be more robust to cohort effects than FI created using cut-points determined by maximum information measures, such as maximal separation of survival curves.

THE CEREBELLUM MAY MITIGATE OBESITY-DRIVEN COGNITIVE IMPAIRMENT IN LATE LIFE

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Mice that overexpress mutant human tau in forebrain neurons develop many features of Alzheimer's disease (AD), including behavioral impairments and neurodegeneration by 5 months of age. While an appropriate model to study AD-like pathology, the transgene's high neurotoxicity makes it difficult to investigate how aging impacts AD onset and progression. The removal of endogenous mouse tau decreases the transgene's neurotoxicity in young mice, which has allowed us to age mice to 20 months of age and investigate behavior at a more AD-relevant stage of life. Interestingly, the tau transgenic mice show increased discrimination between familiar and unfamiliar objects than non-transgenic littermates ($p = 0.02$) suggesting tau transgenic mice have better memory. The transgenic mice also displayed increased physical activity in the Open Field Test than non-transgenic littermates (distance traveled, $p = 0.0102$, and gait speed, $p = 0.0219$). Their improved behavioral performance occurred despite significant forebrain atrophy (20% smaller, $p=0.0003$). Interestingly, the non-transgenic control mice lacking endogenous mouse tau developed insulin resistance and obesity, and had significantly smaller cerebellum than transgenic mice (10% smaller, $p = 0.0007$). These data suggest that insulin resistance and obesity contribute more profoundly to poor behavioral performance than forebrain neurodegeneration. Moreover our study suggests that the cerebellum, recognized primarily for its role in coordination and motor function, may be an important mediator of late life cognitive function, especially in the presence of insulin resistance and obesity.

PRIMING OF MICROGLIA ACTIVITY INCREASES SUSCEPTIBILITY TO DEPRESSION-LIKE BEHAVIORS

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This study investigates the role of microglia activity in stress-induced depression and anxiety and the mechanisms associated with the role of certain microbiome derived anti-inflammatory polyphenols in attenuating stress-induced microglia immune priming and symptoms of depression. We implemented a chronic unpredictable stress (CUS) paradigm to exhibit priming of microglia innate immunity in the context of the onset of depression and anxiety phenotypes. Mechanistic studies related to prophylactic treatment using dietary microbiome derived polyphenols were also investigated in this model. Depression and anxiety phenotypes, gene expression in microglia and protein expression in the cortex of mice were measured following a primary exposure to short-term unpredictable stress (US) followed by CUS. We examined the long-term, persistent CUS induced changes at 4-weeks of post-stress rest following a secondary US exposure. We found depression phenotypes resulted from US only following exposure to CUS. This was accompanied by an increase and persistent upregulation of toll-like receptor 4 (TLR4), RAGE, and HMGB1 gene expression in isolated cortical microglia. Priming by CUS also amplified gene expression of IL-1β in microglia and protein IL-1β in the cerebral cortex following US re-exposure. Increased activity of NF-kB was also noted in the period following CUS. Furthermore, polyphenol treatment prevented stress-induced phenotypes, upregulation of HMGB1, IL-1B, and TLR4 gene expression, as well as upregulation of IL-1β and NF-kB. The study suggests that latent activity of the TLR4-NFkB-IL1β pathway contributes to immune priming and increases susceptibility to depression-like behaviors. Anti-depressant effects of polyphenols may result from their ability to attenuate microglia priming.

TARGETING THE NLRP3 INFLAMMASOME IN MECHANISMS OF SLEEP DEPRIVATION-INDUCED NEUROINFLAMMATION

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The purpose of this study was to determine if inhibitors of innate immunity in microglia could attenuate sleep deprivation (SD)-induced psychological impairment, which involve the assembly and activation of the NLRP3 inflammasome. In the study, CD-1 mice were immune-primed with chronic corticosterone treatment (20 mg/kg IP) for two weeks and were subsequently subjected to one bout of 6 hr SD. Mice were sacrificed immediately afterward to measure cytokine concentrations and caspase-1 activity. We found a significant upregulation of caspase-1 activity in the brain of both mice primed with corticosterone then subjected to sleep deprivation as well as mice only subjected to sleep deprivation ($p < 0.01$). Increased caspase-1 was NLRP3-dependent as treatment with MCC950 (20 mg/kg IP), an inhibitor of NLRP3 inflammasome assembly, completely attenuated SD-induced caspase-1 activity ($p < 0.01$). Additionally, in SD mice we observed increased microglia reactivity as quantified by IBA+ cells and an increased number of microglia that had reactive amoeboid morphologies, as measured through immunohistochemistry. The administration of the NLRP3 specific inhibitor MCC950 similarly prevented SD-induced changes in microglia morphology. The study established that consequential effects of SD- induced inflammasome activation and microglia activation could be prevented by a selective NLRP3 inhibitor. Given the preliminary beneficial effects of targeting NLRP3 in SD, future investigations will establish the clinical efficacy of microbiome-derived polyphenolic compounds, which we have shown provide protection against neuroinflammation in models of stress induced psychological impairment, to attenuate SD neuroinflammation by targeting the NLRP3 inflammasome.