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Topic: AS07 Aging and Neurodegenerative Disorders

SPINAL MORONEURONS' SEX DEPENDENT SIZE AND TYPE CHANGES IN AGING

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A well-known consequence of aging is muscle weakness, the cause of which has long been attributed to muscular atrophy. However, little research has been conducted to investigate if different alpha-motoneuron (α-MN) types experience anatomical changes during aging and whether these changes are sex-dependent. To answer these questions, we measured the size and density of lumbar slow (S), fast fatigue-resistant (FR), fast-intermediate (FI), and fast-fatigable (FF) α-MN types in young (3-4 months), middle-aged (11-13 months), and old (>26 months) male and female C57BL/6 mice. The four α-MN types were identified using immuno-histochemistry labels via novel protocols that we developed. α-MN soma size was measured from the largest 2D cross-sectional area (LCA), and cell density was measured as the number of α-MNs per unit tissue volume. Our results show that α-MNs undergo type and sex-dependent anatomical changes during aging. Specifically, while male and female young α-MNs have similar size, old female α-MNs are smaller than old male cells. For density, female α-MNs had lower cell density than male α-MNs. For α-MN types, larger fast cells, specifically FI, are the most vulnerable in both males and females with FI cells having declining density with aging. As the four α-MN types have never been co-labeled before in mice, these results provide novel data on the anatomical changes α-MN types undergo during aging in males vs. females and provide insights on the cellular mechanisms underlying motor weakness in aging.

Declaration of Interest Statement: None

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TSPO REGULATES HIPPOCAMPAL NEURONAL DEVELOPMENT THROUGH ESTRADIOL/BDNF/NGN3 PATHWAY IN A SEX-DEPENDENT MANNER

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TSPO is involved in the rate-limiting step of de novo neuroactive steroids (NAS) production. Although studies have proved the effects of NAS on neuritogenesis in the hippocampus, none of them have yet investigated the potential role of TSPO in promoting neuronal development, as well as whether TSPO could have sex-dimorphic activities on brain cells. Primary hippocampal neuronal cultures were established using mouse embryos at 17 days of gestation and cultured separately based on sex. TSPO mRNA and protein levels were evaluated on different days *in vitro* (DIVs). To establish the role of TSPO in neuronal development, neurons were treated with the selective TSPO ligands, PK11195, XBD-173, or PIGA1138, or co-treated with the inhibitors aminoglutethimide, letrozole, or k252a, thus morphological analysis was performed. Neuronal TSPO was silenced by nucleoporation and the expression of neuronal markers and of the estradiol-regulated expression of BDNF and Neurogenin3 (Ngn3) were investigated. Sex dimorphisms in neuronal TSPO expression were observed only at the DIV1. Treatment with TSPO ligands increased axon length and branching with major effects in female neurons. Co-treatment with TSPO ligands and inhibitors abolished the effects of TSPO ligands on neuronal development, suggesting the role of estradiol (E2) as an inter-player for TSPO-mediated neuritogenesis. Increased levels of E2, BDNF, and Ngn3 also confirmed the involvement of this cellular pathway. Notably, TSPO silencing affected the expression of neuronal markers related to proper neuronal functions and development only in female neurons, with particular effects on Ngn3 expression. Results show that the regulation of neuronal TSPO activity may occur in a sex-dependent manner. TSPO-mediated regulation of endogenous levels of E2 and of the pro-neural factors BDNF and Ngn3 paves the way for using TSPO as a possible therapeutic target to promote neuronal development and synapse formation.

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REGULATION OF AMYLOID-BETA TRANSPORTERS BY TRANSTHYRETIN - IMPLICATIONS FOR BRAIN PROTECTION AT THE BLOOD-CEREBROSPINAL FLUID BARRIER

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Alzheimer's disease (AD) is characterized by the presence of amyloid-β (Aβ) peptide in extracellular senile plaques. Clearance of Aβ from the brain occurs via transporter proteins such as LRP1, LRP2, RAGE, and Pgp at the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB), the latter established by choroid plexus (CP) epithelial cells. The CP is located in the ventricles and secretes the majority of the CSF. Transthyretin (TTR) is produced in