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POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Palmitoylethanolamide Modulates Gait By Targeting Purkinje Cells in the Brain of Sickle Mice

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Chronic pain is a major comorbidity of sickle cell disease (SCD). Transgenic humanized (BERK) sickle mice recapitulate many clinical features of SCD, including chronic pain. Motor impairments concomitant with increased pyknotic cerebellar Purkinje cells occur in BERK sickle mice. Neurological, neuropathic, and immunological factors, including Purkinje cell damage and chronic inflammation, may contribute to peripheral and central mechanisms that drive gait dysfunction. Pathological changes in Purkinje cells of sickle mice include a significantly greater number of pyknotic cells with smudged nuclei, condensed chromatin, and lack of well-formed nucleoli, & may contribute to alterations in gait as Purkinje cells regulate sensory-motor functions.

Subjects with SCD often use cannabinoids for pain relief, but the intoxicating effects and social stigma associated with their use represent barriers to utilizing this treatment. Palmitoylethanolamide (PEA) is a non-intoxicating endocannabinoid-like lipid mediator naturally produced throughout the body that may act via indirect cannabinoid receptor activation. In clinical studies associated with movement and pain, including chronic arthritic and multiple sclerosis, PEA has demonstrated a reduction of motor dysfunction and pain. Therefore, we examined the effect of PEA on hyperalgesia and gait in humanized HbSS-BERK sickle (HbSS) mice.

We utilized ~6-month-old female, HbSS mice, expressing >99% human α- and ßS- sickle hemoglobin and complete knockout of murine α- and β-globins. Mice were treated with PEA (ip, 20 mg/kg/d) or vehicle (7.5% DMSO, 7.5% Tween 20, in sterile saline) for 2 weeks (2-wks).

Gait measurements were gathered for each mouse at baseline (BL) and 2-wks post treatment during normal walking in Mouse-Walker's transparent corridor with a floor panel mounted with LED lights to produce a detectable touch sensor. Physical contact of paw pads with the surface during natural walking disrupts the light path, causing frustrated total internal reflection detected by a high-speed camera and analyzed using artificial intelligence-based algorithms for gait parameters. Mechanical hyperalgesia was analyzed as paw withdrawal frequency (PWF) in response to 10 applications of 1.0 g von Frey monofilaments. Complete blood counts and brain histopathology on hematoxylin- and eosin-stained sections were evaluated after 2-wks post-treatment.

We observed that PEA ameliorates features of dysfunctional gait in HbSS mice. PEA-treated mice show increased limb swing speed (~30%, $P<0.01$) and shortened swing duration (20%, $P<0.05$) without affecting walking speed ($P>0.05$) Vs. vehicle-treated mice. Also, PEA significantly reduced body instability (~75%, $P<0.05$) and improved stance duration (~65%, $P<0.05$) Vs. BL. This suggests improved limb coordination and reduced sensitivity to mechanical forces during walking. Complementary to gait changes, PEA significantly decreased mechanical hyperalgesia, indicated by lower PWF, 1-hour following initial treatment and following 2-wks post-treatment (~55%, $P< 0.001$ and ~65%, $P< 0.001$, respectively) Vs. BL. PEA decreased the number of circulating white blood cells ($P< 0.05$), with the greatest reduction in circulating lymphocytes ($P< 0.1$). PEA had no adverse effects on organ weight Vs. vehicle treatment. PEA-treated mice showed a significant reduction in pyknotic cerebellar Purkinje cells (~23.9% $p<.006$) in the brain Vs. vehicle. Thus, Purkinje cell pathology may contribute to impaired gait, and PEA may improve motor coordination by reducing Purkinje cell damage.

We provide the first evidence that PEA administration in a humanized sickle mouse model improves features of gait, restores Purkinje cell morphology, and reduces inflammation. Our data demonstrate that PEA may have a disease-modifying effect and restoration of sensory-motor function in SCD. Impairment in gait may also be due to avascular necrosis. Therefore gait

measurements may provide a non-invasive analysis of movement associated pathology and pain as well as effectiveness of targeted interventions.

Disclosures Argueta: *Cyclerion:* Honoraria; *Cayenne Wellness Centers.:* Honoraria.

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