Session 414 - Neurodegeneration and Neuroprotection in Parkinson's Disease

Add To Itinerary

414.04 / S10 - A longitudinal study of PINK1 and PARK7 KO rats

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Presenter at Poster
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Poster

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Disclosures
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Abstract
Epidemiological evidence suggests that exposure to environmental toxicants, such as rotenone are a risk factor for Parkinsons Disease (PD). Rotenone is an industrial pesticide that induces toxicity by affecting complex I mitochondrial function and consequent oxidative damage. Various PD associated genes have also been identified, including Park7 (DJ-1) and Pink1, both of which have a role in mitochondrial homeostasis. Accordingly, both Park7 KO and Pink1 KO rats have been created using Zinc Finger Nuclease (ZFN) technology. A recent report (Dave et al (2014) Neurobiol. Dis. 70: 190-203) described motor changes emerging at 6-8 months age, notably in the Pink1 KO, and evidence for loss of DAergic neurons within the substantia nigra of both KO lines at 8 months. The purpose of the present study was to examine the motor behavioural phenotype of both the Pink1 and Park7 KO lines over a longer timespan (4-20 months age), and to examine the interaction of low dose rotenone administered chronically (3 x 0.5 mg/kg IP/week) on this phenotype. A total of 24 male Park7 KO and 24 Pink1 KO rats entered the study, with 24 of their respective wild type controls, i.e 96 rats in total. Twelve rats from each group received a saline injection 3x weekly, while the other 12 rats received a rotenone injection 3x weekly. Each week from W10 to W88, rats were scored on a simple 5 point scale based on hindlimb and general motor function (0=normal, 4=hindlimb paralysis). Bimonthly neurological assessments were also made, including measures of locomotor activity, beam walking, postural instability. At 20 months (W88) measures of cognitive function (novel object recognition task) and motor response to amphetamine challenge were also taken. The Park7 KO rats developed a modest neurological phenotype over the study duration. At W10 all scores were 0, and by W88, the Park7 KO group was significantly higher than wild type controls with a modest interaction with rotenone treatment (WT+veh: 0$\pm$0; WT+ROT: 0$\pm$0; Park7+VEH: 1.5$\pm$0.3; Park7+ROT: 2.5$\pm$0.4). The Pink1 KO line showed a distinct profile. At W26-32 the Pink1 KO rats had developed a robust neurological phenotype characterized by hindlimb weakness and dragging (e.g. W28 Pink1+VEH: 2.8$\pm$0.2), however by W52 these scores had declined to near WT levels (W52 Pink1+VEH: 0.9$\pm$0.2) suggesting a return of normal hindlimb function. This recovery was also confirmed by other indices of motor function. By W88 neurological scores had increased slightly but were still lower than W26-32. These studies thus characterize the motor phenotype of both KO lines over an extended lifespan and may suggest a subtle interaction between Park7 gene KO and chronic low dose rotenone exposure.