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Reproductive Endocrinology

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Δ-9-tetrahydrocannabinol does not affect motility, morphology or viability, but alters the transcriptome of cryopreserved sperm

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Cannabis is one of the most widely consumed recreational drugs among reproductive aged adults around the globe. It is known that Δ-9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, can interact with the endocannabinoid system (ECS) via cannabinoid receptor 1. Components of the ECS are highly involved in regulating mammalian reproductive processes such as oocyte, sperm, and embryo development by modulating gene expression, apoptosis, and several intracellular pathways. Previous research in our lab demonstrated that THC exposure to bovine oocytes, the ideal translational model for human, was detrimental to in vitro maturation, increased apoptosis in blastomeres and altered gene expression (Misner et al., 2021). Since cannabis consumption is more prevalent among males, we investigated THC effects on male fertility and sperm function. We hypothesized that in vitro THC treatment decreases motility, increases morphological defects, and alters gene expression in sperm. To test this hypothesis, cryopreserved sperm from 5 bulls of known fertility (n=5) was incubated for 6- or 12-hours with concentrations of THC mimicking the plasma levels of THC following therapeutic (0.032μM) and low and high recreational usage (0.32 μM and 3.2 μM) in humans. Bull sperm was used as a translational model since it is highly morphologically similar to human sperm. Sperm motility was assessed manually on a minimum of 100 sperm per treatment group in each bull using a Makler counting chamber and morphology was assessed using Giemsa staining and manual counting of head, neck, midpiece and tail defects of 300 sperm per treatment in each bull. Apoptosis was evaluated

using Annexin V-FITC and PI fluorescent staining coupled with flow cytometry. To evaluate gene expression, RNA from THC-treated sperm was subjected to transcriptome analysis using a GeneChip Bovine Gene 1.0 ST Array. Our results show that THC-treatment at both 6-hours and 12-hours had no influence on sperm motility, contrary to findings in the literature. Furthermore, we also observed no significant effects on sperm morphology and apoptosis following THC-treatment. However, transcriptome analysis identified 39 significantly differentially expressed genes (DEG) following sperm exposure to the lowest concentration of THC, while 196 and 33 genes were differentially expressed following exposure to the mid and high doses correlated with recreational cannabis use, respectively. Upon further analysis of these DEG using DAVID 6.8, several gene ontology and functionally related gene groups were enriched including genes related to nucleosome assembly and function, spermatogenesis, apoptosis and ribosomes and translation. Additional validation of a subset of DEG will be performed using digital droplet PCR. These findings suggest that in vitro THC treatment may cause intracellular and molecular effects, ultimately altering sperm competence, despite not affecting phenotypic characteristics such as motility, morphology or viability (apoptosis).

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