Methods: Twenty-nine controls and 27 participants with schizophrenia completed the study. MRS scanning was conducted on a Philips ‘Achieva’ 7T scanner, and spectra were acquired from a frontal voxel using STEAM (TE/TM/TR=14/33/3000 ms, 128 NEX, 16 NEX water). Participants completed the MATRICS Consensus Cognitive Battery (MCCB) for cognitive function and UCSD Performance-Based Skills Assessment (UPSA) for functional capacity. The relationships between lactate, MCCB, and UPSA were examined. 3T MRs test-retest measures of lactate were conducted on a Siemens Prisma scanner using spectra editing (TE/TR=140/3, editing pulse at 4.1ppm with 30Hz bandwidth, 360 NEX, 16 NEX water).

Results: Patients had significantly higher lactate compared to controls (p = 0.045). Higher lactate was associated with poorer general cognitive function (r=-0.36, p=0.01) Visual learning, processing speed, and reasoning/problem solving cognitive domains showed the strongest relationships with lactate. Poorer functional capacity (r=-0.43, p=0.001) was also related to higher lactate. 3T spectral editing studies showed excellent reproducibility with a mean coefficient of variation of 4%.

Discussion: Higher frontal lactate levels in schizophrenia support the hypothesis that brain bioenergetics are altered and related to cognitive and functional impairments in schizophrenia. Higher lactate could be due to inefficient aerobic metabolism causing a shift towards anaerobic metabolism or poor utilization of lactate. Lactate measurements are doable at 3T field strength and may be a useful biomarker of cognition in schizophrenia. Interventions to promote efficient mitochondrial energy metabolism may prove useful for enhancing cognition and alleviating functional impairments in schizophrenia.

13. ENDOCANNABINOID MODULATION OF DOPAMINE NEUROTRANSMISSION

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Overall Abstract: There are converging lines of evidence that the endocannabinoid system is involved in the pathophysiology of schizophrenia and that understanding these mechanisms may lead to novel treatment targets. In this symposium, we will present a series of experiments that link cannabinoid pharmacology to major fields of schizophrenia research including the dopaminergic, glutamatergic and serotonergic systems, glial cell function and the genetics of cognition.

Dopamine is a major neurotransmitter implicated in the pathophysiology of schizophrenia. Thus, understanding processes that modulate dopaminergic signalling may lead to new insights into the biology and treatment of this disorder. The endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) modulate dopaminergic activity through interactions with CB1 and CB2 receptors. CB1 antagonists inhibit the effects of drugs that potentiate dopaminergic activity, such as cocaine. Similar to CB1 antagonists, CB2 agonists counteract the effects of cocaine in experimental animals. However, the functions of these receptors have been investigated separately. Here we test the hypothesis that CB1 and CB2 receptors interact to ameliorate the behavioural and molecular processes altered under hyperdopaminergic states. We also sought to identify the endocannabinoid involved in these effects.

Methods: Male Swiss mice received cocaine injections to increase dopamine activity in the brain. The biological responses measured were hyperlocomotion, conditioned place preference, cFos expression and Erk protein phosphorylation in the nucleus accumbens. The animals received cannabinoid-related drugs before cocaine injections. The data were analysed with ANOVA followed by the Newman-Keuls test.

Results: The CB1 receptor antagonist, rimonabant, and the CB2 receptor agonist, JWH133, inhibited cocaine-induced hyperlocomotion. Moreover, the CB2 antagonist, AM630, reversed the inhibitory effects of rimonabant in cocaine-induced hyperlocomotion, cFos expression, Erk phosphorylation and conditioned place preference. The inhibitors of anandamide and 2-AG hydrolysis, URB597 (FAAH inhibitor) and JZL184 (MGL inhibitor), respectively, were ineffective in inhibiting cocaine hyperlocomotion. However, when combined with a sub-effective dose of rimonabant, JZL184 (but not URB597), inhibited cocaine effects.

Discussion: A CB2 antagonist reversed the effect of a CB1 antagonist, suggesting that these receptors modulate cocaine effects in opposite ways. Accordingly, increasing brain 2-AG levels inhibited cocaine effects only if CB1 is blocked and CB2 available. Thus, selective activation of CB2 receptors warrants further investigation as a new strategy for the treatment of psychiatric disorders resulting from hyperdopaminergic states.

13.2 CANNABIDIOL AS AN ANTIPSYCHOTIC DRUG

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Background: The phytocannabinoid cannabidiol (CBD) attenuates the psychotomimetic effects produced by high doses of delta-9-tetrahydrocannabinol (THC), the main component of the Cannabis sativa plant.

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Thus, the effects of cannabinoid drugs on these cells may contribute to our understanding of the pathobiology of schizophrenia. Specifically, oligodendrocytes are associated with white matter deficits in schizophrenia. The modulation of their function, survival, and differentiation can result in new approaches to treat schizophrenia’s white matter-associated deficits. Here we have investigated the effects of cannabidiol (CBD) on a human oligodendrocyte culture (MO3.13) in terms of protein expression.

**Methods:** MO3.13 oligodendrocytes were treated with CBD (1µM) for 8h. Proteins were extracted from these cells, digested, and processed in a state-of-the-art LC-MS/MS system. Quantitative proteomics approaches were then employed in a label-free fashion. Differentially expressed proteins among the CBD treatment and controls were analyzed using systems biology in silico tools.

**Results:** Analyses identified that several proteins were up- or down-regulated in response to CBD treatment. These proteins were analyzed in terms of biological processes, pathways, and functions. CBD affected the expression of 136 proteins. Some proteins such as the transient receptor potential channel (TRPM7), microtubule-associated proteins (MAP2 and MAP4), Rho GTPase activating proteins (21 and 23), and calcium channel voltage-dependent T type alpha 1H (CACNA1H), among others possibly involved in schizophrenia pathobiology, were increased by CBD-treatment.

**Discussion:** Studies have shown the effects of CBD on the treatment of schizophrenia; but the mechanisms involved in its antipsychotic properties are not fully understood. Herein, we observed that CBD modulated the expression of proteins that can be implicated in schizophrenia pathobiology. For instance, MAPs functions are related to cytoskeleton organization, differentiation, and migration of oligodendrocytes. Studies have shown a decrease of MAPs in schizophrenia patients; thus, increasing MAP2 and MAP4 by CBD may be an interesting mechanism to treat and prevent cytoskeleton impairments in oligodendrocytes and neurons in schizophrenia. Moreover, CBD increased the voltage gated channel (CACNA1H) that is involved in cannabionoid retrograde signaling and glutamate and GABAergic neurotransmission. CACNA1H modulates Ca2+ levels and the synaptic vesicle cycle. To note, we also found effects of CBD on pathways and biological processes involved with schizophrenia pathobiology, such as glucose metabolism, axon guidance, and inflammation mediated by cytokine signaling. In summary, these proteomic findings may provide an integrated picture of the role of endocannabinoid signaling in oligodendrocyte cells and possible implications for schizophrenia’s pathobiology.

### 13.3 EFFETS OF CANNABINIODS ON A HUMAN OLIGODENDROCYTE CULTURE: IMPLICATIONS FOR SCHIZOPHRENIA

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**Background:** Preclinical studies have suggested the involvement of the endocannabinoid system in schizophrenia pathobiology. The effects of cannabinoid drugs in several animal models for schizophrenia have been used to understand the pathology of the disease, and to investigate potential treatments for schizophrenia symptoms. Alterations in endocannabinoid (eCB) signaling, such as cannabinoid receptor expression and anandamide levels, have also been investigated in animal models. In addition, in vitro studies have shown the molecular pathways and biological processes associated with cannabinoids’ effects in some cell types, such as glial cell cultures. Glial cells, which express cannabinoid CB1 and CB2 receptors and synthesize eCBs, have been shown to be implicated in schizophrenia. Thus, the effects of cannabinoid drugs on these cells may contribute to our knowledge about the pathobiology of schizophrenia. Specifically, oligodendrocytes are associated with white matter deficits in schizophrenia. The modulation of their function, survival, and differentiation can result in new approaches to treat schizophrenia’s white matter-associated deficits. Here we have investigated the effects of cannabidiol (CBD) on a human oligodendrocyte culture (MO3.13) in terms of protein expression.

**Methods:** MO3.13 oligodendrocytes were treated with CBD (1µM) for 8h. Proteins were extracted from these cells, digested, and processed in a state-of-the-art LC-MS/MS system. Quantitative proteomics approaches were then employed in a label-free fashion. Differentially expressed proteins among the CBD treatment and controls were analyzed using systems biology in silico tools.

**Results:** Analyses identified that several proteins were up- or down-regulated in response to CBD treatment. These proteins were analyzed in terms of biological processes, pathways, and functions. CBD affected the expression of 136 proteins. Some proteins such as the transient receptor potential channel (TRPM7), microtubule-associated proteins (MAP2 and MAP4), Rho GTPase activating proteins (21 and 23), and calcium channel voltage-dependent T type alpha 1H (CACNA1H), among others possibly involved in schizophrenia pathobiology, were increased by CBD-treatment.

**Discussion:** Studies have shown the effects of CBD on the treatment of schizophrenia; but the mechanisms involved in its antipsychotic properties are not fully understood. Herein, we observed that CBD modulated the expression of proteins that can be implicated in schizophrenia pathobiology. For instance, MAPs functions are related to cytoskeleton organization, differentiation, and migration of oligodendrocytes. Studies have shown a decrease of MAPs in schizophrenia patients; thus, increasing MAP2 and MAP4 by CBD may be an interesting mechanism to treat and prevent cytoskeleton impairments in oligodendrocytes and neurons in schizophrenia. Moreover, CBD increased the voltage gated channel (CACNA1H) that is involved in cannabionoid retrograde signaling and glutamate and GABAergic neurotransmission. CACNA1H modulates Ca2+ levels and the synaptic vesicle cycle. To note, we also found effects of CBD on pathways and biological processes involved with schizophrenia pathobiology, such as glucose metabolism, axon guidance, and inflammation mediated by cytokine signaling. In summary, these proteomic findings may provide an integrated picture of the role of endocannabinoid signaling in oligodendrocyte cells and possible implications for schizophrenia’s pathobiology.

### 13.4 CANNABINOID RECEPTOR GENE POLYMORPHISMS AND COGNITIVE PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA

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**Background:** Cognition is a major determinant of functioning in patients with schizophrenia. There is evidence that the endocannabinoid system influences cognition in human subjects, and participates in the pathophysiology of schizophrenia. In a previous study, we have shown that the expression of cannabinoid receptors (CB1R and CB2R) on peripheral lymphocytes is inversely correlated with performance in the Brief Assessment of Cognition in Schizophrenia (BACS), in patients with schizophrenia. Recently, CBrs polymorphisms have been associated with an increased risk for schizophrenia, structural changes in the central nervous systems and in cognitive performance of the patients. The aim of the present study was to investigate the association between CBs polymorphisms and cognitive performance as assessed by the BACS.

**Methods:** A sample of 85 stable medicated patients (61m; age = 41.6 ± 12.2 years; illness duration = 12.8 ± 10.7 years) was enrolled in this study. Two CB1R polymorphisms (rs1049353; rs12720071) and one CB2R polymorphism (rs2229579) were tested.

**Conclusion:** Cognition is a major determinant of functioning in patients with schizophrenia. There is evidence that the endocannabinoid system influences cognition in human subjects, and participates in the pathophysiology of schizophrenia. In a previous study, we have shown that the expression of cannabinoid receptors (CB1R and CB2R) on peripheral lymphocytes is inversely correlated with performance in the Brief Assessment of Cognition in Schizophrenia (BACS), in patients with schizophrenia. Recently, CBRS polymorphisms have been associated with an increased risk for schizophrenia, structural changes in the central nervous systems and in cognitive performance of the patients. The aim of the present study was to investigate the association between CBRS polymorphisms and cognitive performance as assessed by the BACS.

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