Corroborating this effect, several preclinical and clinical studies indicate that CBD has antipsychotic properties. The mechanisms responsible for these properties, however, remain unknown (Campos et al., Philos Trans R Soc Lond B Biol Sci 367:3364–782013). We have recently found that repeated CBD administration prevents the behavioral impairments, measured in the pre-pulse inhibition, social interaction and novel object recognition tests, induced in mice by repeated treatment (28 days) with the NMDA receptor antagonist MK-801. CBD also prevented the neural (measured by delta-FosB) and microglia activation, and the decrease in the number of parvalbumin-positive neurons, observed in the medial prefrontal cortex (Gomes et al., Int J Neuropsychopharmacol 18(5)2014, Schizophr Res 164:155–63, 2015). Currently, we are investigating if CBD could also reverse these changes once they have been established and the possible mechanisms of this effect.

Methods: Male C57BL/6J mice received intraperitoneal injections of MK-801 (0.25, 0.5 or 1 mg/kg, twice a day) for 7 or 14 days. To determine if these treatments regime would induce acute and long-term deficits, the social interaction (SI) test was performed 1 or 8 days after the end of the MK-801 treatment. Twenty-four hours after the SI, animals were submitted to the novel object recognition (NOR) test. Having established that 14 days of MK-801 induce both acute (24 h after) and long-term (8 days after) behavioral deficits in the SI and NOR tests, we investigated if repeated treatment with CBD (15, 30 or 60 mg/kg daily, i.p.) would reverse these changes. CBD treatment began 24h after the end of the MK-801 treatment and lasted for 7 days. Repeated clozapine (1 mg/kg) was used as a positive control. Forty-eight hours after the last injection, animals were submitted to SI and, 24-h later, to the NOR test. In a second experiment, independent groups of mice received, before each CBD injection, AM251 (a CB1 receptor inverse agonist, 0.1–0.3 mg/kg), AM630 (a CB2 receptor inverse agonist, 0.1–0.3 mg/kg), or the 5HT1A receptor antagonist WAY100635 (0.1–0.3 mg/kg). The data were analyzed by ANOVA followed by the Newman-Keuls test.

Results: MK-801 (0.5 mg/kg) administration for 14 days, but not for 7 days, impaired SI and NOR. Repeated CBD or clozapine treatment reversed these impairments. CB1 and CB2 antagonists (AM251 and AM630, respectively) failed to change CBD effect. However, its effect was blocked by pretreatment with the 5HT1A receptor antagonist WAY100635.

Discussion: Our findings show that a 2-week treatment with the NMDA receptor antagonist MK801 impairs social interaction and novel object recognition, which have been associated with negative and cognitive symptoms of schizophrenia, respectively. These behavioral deficits last for at least one week and are reversed by the atypical antipsychotic clozapine or CBD, reinforcing the proposal that this latter drug has antipsychotic-like properties. CBD effects seem to depend on facilitation of 5HT1A-mediated neurotransmission.

13.3 EFFECTS OF CANNABINOIDS 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 cannabinoids 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 cannabinoid 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 CBRS polymorphisms and cognitive performance as assessed by the BACS.

Methods: A sample of 85 stable medicated patients (61% men; 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.
Results: We did not find any difference in general cognitive performance (BACS total score) regarding the three polymorphisms tested. However, when we analysed specific cognitive domains we have found a significant difference (p=0.002) regarding working memory (assessed by the Digit Span test) in patients with the rs12720071 polymorphism, where those with allele C performed better than those with T/T genotype. Since about a third of the patients (34%) had a history of past use of cannabis and 2.5% reported current use, we performed the rs12720071 polymorphism analysis excluding these patients. In this subgroup of patients, those with allele C also performed significantly better on Digit Span test (p=0.037).

Discussion: In this study, the rs12720071 polymorphism of CB1R appears to influence performance on a working memory task that is sensitive to prefrontal cortex function.

14. VIOLENCE IN SCHIZOPHRENIA: PREVALENCE, MEASUREMENT, PREDICTION AND PREVENTION

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Overall Abstract: Most patients with schizophrenia and bipolar disorders (severe mental illness, SMI) are not violent in their lifetimes, however, a minority of patients are violent at some points in the course of their illness. As the illness appears relatively early in life, and typically runs a chronic course, the number of violent incidents caused by patients can be considerable in some cases. Due to the stigma toward SMI, the media often emphasize reporting of these incidents, which fuel the stigma even more. Although violent behavior is a common cause of concern for patients, their families and clinicians, it is not often discussed in scientific meetings. The purpose of this symposium is to bring this relatively neglected, but very important topic into the spotlight in SIRS, in order to summarize the latest evidence for clinicians and researchers, and to foster new work on reducing these risks of violence.

Dr. Weiser will present an overview of the prevalence of violent behavior in patients with SMI, and will present a population-based, case-control study from Israel, showing increased rates of violent crime in patients with SMI, particularly in female patients and patients who abuse drugs. Secondary analyses will show increased rates of violent behaviour in siblings of patients as well.

Dr. Fazel will present a systematic review on the prognostic (or predictive) accuracy of structured ways to assess violence risk in patients with severe mental illness, and present new work on a scalable and potentially useful predictive model of violent behaviour based on 75,000 patients in Sweden. Dr. Nijman will present a model based on patient, ward and staff variables focused on the causes and triggers of aggressive behavior on (locked) psychiatric wards. Based on this model, a number of preventive measures can be formulated. At the patient level, the administration of anti-psychotic medication is used to reduce the negative cognitive schemes and delusional thoughts that are depicted in the center of the model. A more novel intervention at the patient level may be the additional administration of nutritional supplements with (among others) high levels of omega 3 fatty acids. The results of two Dutch studies on this topic will be briefly presented in the lecture, among which a RCT on the effects of the use of nutritional supplements on aggressiveness. On the staff level, the use of short-term (daily) risks assessments by the ward nursing staff, among others by means of the six item Brøset Violence Checklist (BVC), has been found to reduce aggressiveness as well as the use of coercive measures on psychiatric wards in two cluster randomized RCTs. On the ward level, studies indicate that aggressiveness on psychiatric wards can be reduced by preventing overcrowding on psychiatric wards, and by providing more space and privacy to the patients.

He will then present data on the effect of extended conditional release, Forensic Assertive Community Treatment (FACT) teams, and Psychiatric Security Review Boards on re-arrest rates.

14.1 VIOLENT CRIME IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A POPULATION-BASED STUDY

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Background: Previous studies have found that patients with schizophrenia and bipolar disorder are more likely to be violent than the general population. The aim of this study was to investigate the association between schizophrenia and bipolar disorder and violent crime in the Israeli population.

Methods: Using the Israeli Psychiatric Hospitalization Case Registry we identified 3187 patients with a discharge diagnosis of schizophrenia and 506 patients with a discharge diagnosis of bipolar disorder. For each proband we identified parents and siblings, and gender-and age-matched controls for patients, parents and siblings. Information on violent crimes was obtained from police records.

Results: Patients with schizophrenia were at increased risk for violent crimes compared with controls [odds ratio (OR) 4.3, 95% confidence interval (CI) 3.8–4.9], especially women (OR 9.9, 95% CI 6.2–15.7). Risk for violent crimes was higher among patients with co-morbid substance misuse than in patients without such co-morbidity (OR 5.1, 95% CI 4.2–6.3). Patients with diagnosis of bipolar disorder were 2.5 times more likely to be convicted or released for mental reasons of violent crimes compared with controls and unaffected full siblings (OR=2.5, 95%CI 1.7–3.7, OR=2.5, 95%CI 1.6–4.0 respectively). Although men were more violent than women, diagnosis of bipolar disorder was a more significant risk factor for female patients than for male patients (OR=16.1 95%CI 1.8–144.6 vs. OR=2.4, 95%CI 1.5–3.7).

Discussion: The results of this study suggest that increased risk of violence is part of the clinical picture of schizophrenia and bipolar disorder and needs to be recognized as a legitimate, essential, aspect of clinical management.

14.2 SUCTURED RISK ASSESSMENT IN PSYCHIATRY

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Background: Current approaches to stratify psychiatric patients into groups based on risk of violence are limited by inconsistency, variable accuracy, and unscalability.

Methods: Based on a national cohort of 75 158 Swedish individuals aged 15–65 with a diagnosis of severe mental illness (schizophrenic-spectrum and bipolar disorders) with 574 018 patient episodes, we developed predictive models for violent offending through linkage of population-based registers. First, a derivation model was developed to determine strength of pre-specified criminal history, socio-demographic, and clinical risk factors, and tested it in external validation. We measured discrimination and calibration for prediction of violent offending at 1 year using specified risk cut-offs.

Results: A 16 item model was developed from criminal history, socio-demographic and clinical risk factors, which are mostly routinely collected. In external validation, the model showed good measures of