Methods: We affinity purified PSD95 protein complexes from GluN1KD and WT brains (n=3 per group) and ran each sample through our liquid chromatography tandem mass spectrometry (LC-MS/MS) protocol in duplicate. We performed pathway analysis with the EnRICHr suite of bioinformatic tools and compared WT to GluN1KD PSD95 interactomes using the top 20 differentially expressed proteins. We also studied how NMDA receptor hypofunction changes the expression of genes related to glucose metabolism and bioenergetics by quantitative PCR of brain cDNA from WT and GluN1 knockout mice.

Results: Pathway analysis revealed that WT mice showed pathways relevant for synaptic plasticity (as expected), while GluN1KD analyses yielded proteins related to glucose metabolism and utilization. Gene expression analysis revealed that GluN1 knockout mice have significant decreases in the expression of SLC16A3, SLC2A1, and SLC2A3, which are the genes for the monocarboxylate transporter (MCT4), and glucose transporters 1 and 3 (GLUT1 and GLUT3).

Discussion: Our results show that NMDA receptor dysfunction leads to expression changes that would reduce glucose and lactate transport into neurons. The synaptic proteome of NMDAR deficient mice shows an increase in glycolytic enzymes located at the synapse. These data suggest a profound shift in the composition of the cortical excitatory synaptic proteome in GluN1KD mice, with apparent increases in neuronal substrates in neurons. At the same time, there were significant decreases in the levels of transporters that bring glucose and the primary energy substrate, lactate, into neurons. The MCT4 shuttles lactate from astrocytes to neurons, which can then be used for oxidative respiration in neurons. GLUT1, is responsible for transport of glucose across the blood-brain-barrier, and GLUT3 is expressed on neurons and is responsible for glucose uptake in those cells. Notably, we have identified that these transporter gene transcripts are reduced in post-mortem brains of people with schizophrenia. Thus, this mouse may be a useful tool to model bioenergetic changes that are observed in schizophrenia, and study functional outcomes when glucose metabolism is improved.

12.3 SYSTEM XC- AS A NOVEL MODULATOR OF CORTICOSTRIATAL NEUROTRANSMISSION

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Background: System xc- is a plasma membrane amino acid antiporter, of mainly glial origin, that couples the import of cystine with the export of glutamate. System xc- (specific subunit xCT) contributes substantially to ambient extracellular glutamate levels in various regions of the brain, including the striatum and hippocampus. Despite the fact that system xc- is highly expressed in the brain and is a proposed therapeutic target for various neurological disorders, its function under physiological conditions in the central nervous system remains poorly understood. By acting as a source of glial extrasynaptic glutamate, system xc- might modulate synaptic transmission as a mechanism of neuro-glial communication. Previous electrophysiological findings indicate that system xc- delivered glutamate can inhibit excitatory synaptic neurotransmission in the corticostriatal pathway and at hippocampal CA3-CA1 synapses. To gain further insight into the proposed function of system xc- as modulator of synaptic transmission, we here focus on corticostriatal synapses.

Methods: Single section electron microscopy was carried out on VGLUT1-pre-embedded and glutamate immunogold post-embedded labeled slices of the dorsolateral striatum of xCT-/- and xCT+/- mice. Various parameters related to the pre- and post-synaptic compartments were integrated on the obtained electron micrographs, including glutamate immunogold density in the presynaptic terminal and spine, area of the terminal and spine, measures of the postsynaptic density (PSD) (length, area, thickness, and maximum thickness), percentage of PSDs showing perforations, and width of the synaptic cleft. Electrophysiological measures of corticostriatal transmission were obtained by recording the amplitude of field excitatory postsynaptic potentials (fEPSPs) after stimulation of corticostriatal fibers. Finally, grooming behavior was compared between xCT-/- and xCT+/- littermates.

Results: Genetic deletion of xCT led to depletion of glutamate immunogold labeling from corticostriatal terminals and their corresponding dendritic spines. Absence of xCT did not, however, affect the morphology of corticostriatal synapses, as evaluated by the area of the terminals and spines, size of the PSD, and width of the synaptic cleft. Similarly, no changes could be observed in the density of VGLUT1-positive synapses, indicating normal cortical innervation and spine density. Electrophysiological recordings revealed decreased amplitude of fEPSPs in xCT-/- mice after stimulation of corticostriatal fibers. Preliminary investigations revealed that this reduced response can be rescued by restoring physiological levels of glutamate to xCT-/- slices. Changes in corticostriatal transmission were not reflected in aberrant grooming behavior in xCT-/- mice; we could not observe any difference in the total grooming duration, the number of grooming bouts, the average bout duration or the latency to onset to grooming between xCT-/- and xCT+/- mice.

Discussion: Contrary to available evidence at hippocampal and corticostriatal pathways, our findings indicate a positive effect of system xc- on basal synaptic transmission at corticostriatal synapses. The decreased response we observed after stimulation of corticostriatal fibers in xCT-/- mice was accompanied by depletion of glutamate immunogold labeling from corticostriatal terminals, suggesting a possible defect in presynaptic glutamate handling. Given the strong decrease (70%) in extracellular glutamate levels previously reported in this strain of mice, we hypothesize that the decreased presynaptic glutamate labeling in xCT-/- mice is related to a loss of extracellular glutamate needed to supply terminals for proper excitatory transmission. This hypothesis is supported by our preliminary results showing increased responses in xCT-/- slices after restoring physiological levels of glutamate. Together, our findings shed new light on the role of system xc- in controlling synaptic transmission, and suggest that it may play an important role in supplying presynaptic terminals with glutamate as an alternative mechanism to the glutamate-glutamine cycle. As a novel modulator of corticostriatal transmission, system xc- may be of interest as a possible therapeutic target for disorders with a corticostriatal component, such as schizophrenia or obsessive-compulsive disorder.

12.4 BRAIN LACTATE IS RELATED TO COGNITION IN SCHIZOPHRENIA

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Next, we will describe the effects of CBD on glial cells. Glial cells, which express CB1 and CB2 receptors and synthesise endocannabinoid transmitter, have been implicated in schizophrenia whereby oligodendrocyte dysfunction has been associated with white matter deficits in the illness. In an investigation of the effects of CBD on a human oligodendrocyte culture (MO3.13), CBD administration resulted in diverse changes in the expression of proteins implicated in the pathophysiology of schizophrenia.

Finally, we provide further evidence that polymorphisms in cannabinoid receptor genes are associated with cognitive impairments in humans. In particular, the rs12720071 polymorphism T/T allele is associated with impaired working memory in patients with psychosis.

13.1 ENDOCANNABINOID MODULATION OF DOPAMINE NEUROTRANSMISSION

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Background: Dopamine is the major neurotransmitter implicated in schizophrenia pathology. Thus, understanding the processes modulating dopaminergic signalling may lead to new insights in the biology and treatment of this disorder. The endocannabinoids anandamide and 2-arachidonoylglicerol (2-AG) modulate neural activity through interactions CB1 and CB2 receptors. CB1 antagonists inhibit the effects of drugs that facilitate dopamine 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 ANTI精神病OTIC 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.