

therapeutics mainly target the positive symptoms, cognitive symptoms are often not effectively treated. Our recent discovery that mGlu3 and mGlu5 can act as signaling partners to modulate synaptic plasticity in the prefrontal cortex led us to hypothesize that mGlu3 may subserve similar functions to those of mGlu5 during hippocampal synaptic plasticity and hippocampal-dependent behaviors.

Methods: We directly tested this hypothesis using acute slice electrophysiology to investigate basal synaptic transmission as well as long-term plasticity in hippocampal slices. To test cognition, the associative fear learning behavioral assay, termed trace-fear conditioning, was used. C57bl/6 mice or CaMKII-cre;mGlu5^{-/-} mice were used in all studies.

Results: We report that mGlu2/3 activation enhances hippocampal theta-burst (TBS)-induced LTP but was without effect on group I mGlu agonist-induced LTD. The group II mGlu agonist enhancement of TBS-LTP was blocked by antagonists of mGlu3 or mGlu5.

We next tested downstream mechanisms of group II mGlu induced LTP by chemically activating LTP with the group II agonist LY379268 in combination with selective antagonists. We verified the LTP was induced by mGlu3 activation but not mGlu2 using selective negative allosteric modulators of each subtype. Furthermore, mGlu5 negative allosteric modulation with MTEP blocked mGlu3-LTP, and conversely the mGlu5 positive allosteric modulator, VU0092273, enhanced mGlu3-LTP. The cannabinoid receptor type 1 antagonist AM251 was also capable of blocking mGlu3-LTP, suggesting cannabinoid signaling mechanistically drives this LTP.

Having confirmed a role for mGlu5 in the mGlu3-LTP, we next verified that postsynaptic mGlu5 located on pyramidal neurons was necessary for mGlu3-LTP by utilizing CaMKII-cre;mGlu5^{-/-} mice. It was found that hippocampal slices from these mice showed no enhancement of LTP when LY379268 was bath applied alone or in combination with TBS-stimulation. Behaviorally, we discovered that selective activation of mGlu3 by systemically injecting the group II mGlu agonist in combination with a selective mGlu2 negative allosteric modulator, VU6001966, causes an enhancement in the acquisition of trace-fear conditioning learning. This was also confirmed to be dependent on mGlu5 as both systemic pharmacological inhibition or genetic deletion of mGlu5 abolished this learning enhancement. Further testing of the ability of mGlu3 activation to augment other cognitive tasks is currently underway.

Discussion: These results taken together demonstrate mGlu3 enhances hippocampal LTP and hippocampal-dependent learning through mechanisms that involve both mGlu5 and CB1 receptor activation. This work provides a basic biological mechanism and preclinical therapeutic validation for mGlu3 as a target for neurological disorders in which cognition is disrupted such as schizophrenia.

T40. GPR52 AGONISTS REPRESENT A NOVEL APPROACH TO TREAT UNMET MEDICAL NEED IN SCHIZOPHRENIA

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Background: There are currently no treatment options for key symptom domains in certain psychiatric and neurological diseases. For example, antipsychotics effectively treat the positive symptoms of schizophrenia, however both the cognitive impairments associated with schizophrenia (CIAS) and negative symptoms, both key predictors of functional outcome, are not treated by current therapies. Additionally, psychotic symptoms associated with neurological diseases such as Alzheimer's Disease (AD) are not adequately treated with current antipsychotics. Therefore, novel mechanisms to address these unmet medical needs are urgently required and are under investigation.

GPR52 is a Gs-coupled orphan g-protein coupled receptor which has an intriguing pattern of brain expression. In cortex, GPR52 is expressed

primarily on glutamatergic neurons and co-localized with the Gs-coupled D1 receptor (D1R). Deficiencies in D1R activation are associated with both cognitive deficit and negative symptoms of schizophrenia. In contrast, in the striatum, GPR52 is almost exclusively co-expressed with the Gi-coupled D2 receptor (D2R), which mediates the reduction in positive symptoms by antipsychotics. Based on GPR52's functional coupling and co-localization, agonists may be predicted to resemble D1R agonists in cortical regions, thus treating cognitive or negative symptoms, while resembling D2R antagonists in striatal regions. Thus, GPR52 agonists have the potential to provide a novel therapeutic strategy for the currently untreated CIAS and negative symptom domains in addition to the psychotic symptoms of AD.

Methods: To assess the antipsychotic potential of GPR52 agonists, they were tested for their ability to decrease psychostimulant-induced hyperlocomotion. The efficacy of GPR52 agonists for CIAS and sociability, an aspect of negative symptoms, was assessed in the sub-chronic phencyclidine (scPCP) model for schizophrenia, known to induce long-lasting cognitive and social behaviour deficits, in addition to a reduction in parvalbumin-positive GABAergic interneurons in hippocampus and pre-frontal cortex. Rats were treated with PCP twice daily for 7 days followed by 7 days wash-out and then tested in the attentional set shifting task (ASST) for executive function and the social interaction test for sociability respectively following treatment with a GPR52 agonist.

Results: GPR52 agonist 1 dose-dependently reversed psychostimulant-induced hyperlocomotion in rats at doses which were behaviorally quiescent when administered alone. Additionally, GPR52 agonist 2 showed a robust, dose-dependent rescue of scPCP induced deficits in the extra dimensional shift phase of the ASST, achieving significance after a 4 mg/kg p.o. application. Likewise, GPR52 agonist 2 significantly rescued scPCP induced deficits in social interaction at identical doses as in ASST without effects on object exploration or locomotor activity.

Discussion: GPR52 agonists were efficacious in animal models assessing the three main symptom domains associated with schizophrenia. Efficacy in ASST and SI demonstrate both pro-cognitive efficacy and restoration of an aspect of negative symptoms, respectively, in a well-established model inducing behavioral and neuropathological deficits associated with schizophrenia. Furthermore, GPR52 agonists reduced psychostimulant-induced hyperlocomotion, an effect associated with antipsychotic efficacy. Taken together, these data demonstrate the potential of this innovative mechanism to simultaneously treat the three core symptoms domains of schizophrenia as well as potentially treat the psychotic symptoms associated with other neurological disorders.

T41. MODIFIED COGNITIVE BEHAVIORAL THERAPY FOR ELDERLY PATIENTS WITH SCHIZOPHRENIA: A RANDOMIZED, CONTROLLED PILOT TRIAL

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Background: An European society growing older sets the need to explore treatment options for elderly patients. Here we aimed to gather evidence on the effectiveness of a modified cognitive behavioural therapy (mCBT) in elderly schizophrenia patients as compared to treatment as usual (TAU).

Methods: 43 schizophrenia patients > 55y (mean 60 y), were assessed in a randomized, single blind controlled pilot trial with parallel groups: TAU+mCBT vs. TAU and intention to treat (ITT) last observation carried forward (LOCF) analysis. Subjects were recruited in Germany among