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BACOPA MONNIERI (BRAHMI) CAN RECOVER AND PREVENT COGNITIVE DEFICIT IN SUB-CHRONIC PHENCYCLIDINE RAT MODEL OF SCHIZOPHRENIA BY ELEVATING VESICULAR GLUTAMATE TRANSPORTER TYPE 3 IN THE BRAIN
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Abstract
Background: Glutamatergic hypofunction is implicated in schizophrenia. Reduced presynaptic glutamatergic markers, remarkably vesicular glutamate transporter type 1 (VGLUT1) and 2 (VGLUT2) indicates glutamatergic deficit leading to cognitive impairment in schizophrenia. However, few studies in VGLUT3 have been reported. Brahmi (Bacopa monnieri), a traditional herbal medicine, might be a new treatment and prevention for cognitive deficit in schizophrenia by changing cerebral VGLUT3 density.

Objective: To study cognitive enhancement- and neuroprotective effects of Brahmi on novel object recognition task and cerebral VGLUT3 immunodensity in sub-chronic phencyclidine (PCP) rat model of schizophrenia.

Material and Method: Cognitive enhancement effect study; rats were assigned to three groups; Group-1: Control, Group-2: PCP-administration, Group-3: PCP + Brahmi. Neuroprotective effect study; rats were assigned to three groups; Group-1: Control, Group-2: PCP-administration, Group-3: Brahmi + PCP. Discrimination ratio (DR) representing cognitive ability was obtained from novel object recognition task. VGLUT3 immunodensity was measured in prefrontal cortex, striatum and cornu ammonis fields 1–3 (CA1-3) of hippocampus using immunohistochemistry.

Results: DR was significantly reduced in PCP group compared with control. This occurred alongside VGLUT3 reduction in prefrontal cortex, striatum and CA1-3. PCP + Brahmi showed a higher DR score compared with PCP alone and this occurred alongside a significantly increased VGLUT3 immunodensity in prefrontal cortex and striatum. Brahmi + PCP group also showed a higher DR score compared with PCP alone and this occurred alongside a significantly increased VGLUT3 immunodensity in prefrontal cortex, striatum and CA1-3.

Conclusion: Reduced cerebral VGLUT3 produced cognitive deficit in rats receiving PCP. Interestingly, receiving Brahmi after PCP administration can restore this cognitive deficit by increasing VGLUT3 in prefrontal cortex and striatum. Receiving Brahmi before PCP administration can also prevent cognitive impairment by elevating VGLUT3 in prefrontal cortex, striatum and CA1-3. Therefore, Brahmi could be a new frontier of restoration and prevention of cognitive deficit in schizophrenia.

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GPR52 agonists show pro-cognitive properties
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Abstract
GPR52 is an orphan G protein-coupled receptor which is mainly expressed in the brain and shows a unique co-expression profile. In the striatum it is expressed almost exclusively in neurons also expressing D2-like dopamine receptors, whereas in the cortex it mainly co-expresses with the D1-like dopamine receptor. Because GPR52 is Gs-coupled, this has led to the prediction that agonists of GPR52 may have both antipsychotic and pro-cognitive properties by their action in the striatum and the prefrontal cortex, respectively. This makes GPR52 a particularly interesting target for the treatment of schizophrenia. While tool compounds have, indeed, been shown to reverse pharmacologically induced striatal hyperdopaminergic states, direct evidence for their efficacy in cognition was lacking. Here, we show data from in vitro, ex vivo and in vivo studies strongly supporting the hypothesized pro-cognitive efficacy.

Tool compounds were synthesized following Takeda patents WO2010/018874, WO2011/093352 and WO2012/020738 and their in vitro efficacy was confirmed in stably transfected HEK cells. The compounds led to a robust increase of intracellular cAMP concentrations, with an EC50 of 30nM for the tool compound chosen for further characterization. To test the hypothesis that this increase in cAMP affects synaptic transmission in the prefrontal cortex, layer V responses to layer II stimulation were measured in prefrontal cortical rat brain slices. Bath application of the tool compound led to a robust and sustained increase in excitatory post-synaptic potentials, suggesting the possibility of pro-cognitive efficacy. To test this, working memory performance was measured in mice in the T-maze spontaneous alternation task. The deficit induced by the NMDA receptor antagonist MK-801 was dose-dependently reversed by the administration of the GPR52 tool compound agonist.

Together, these data show that GPR52 agonists also have potential for treatment of cognitive symptoms in psychiatric disorders characterized by cortical dopaminergic or glutamatergic hypofunction, such as schizophrenia.