NEUROANATOMY

Hippocampal-prefrontal coherence linked to schizophrenia in mice could point to a potential psychosis treatment

Abnormalities in hippocampal-prefrontal theta coherence played a role in the dysfunctional regulation of selective attention through short-term habituation leading to aberrant salience. Introducing the AMPA receptor subunit GLUA1 in the CA2/CA3 of the hippocampus in Gria1-deficient mice restored hippocampal-prefrontal coherence, linking GRIA1 to schizophrenia[1].

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The study conducted by Bygrave and colleagues supported a link between the lack of the gene GRIA1 in the hippocampus of mice brains and elevated levels of hippocampal-prefrontal theta coherence which underlined deficits in short-term habituation and could lead to aberrant salience, a player in schizophrenic patients exhibiting psychosis[1]. Variations of the GRIA1 gene encode AMPA receptors that reside in the central nervous system and are important for transmitting excitatory signals between neurons[2]. Previous research has concluded that dysfunctional AMPA receptors are associated with positive symptoms of schizophrenia such as hallucinations and delusions, thereby supporting the link between the schizophrenia and GRIA1[2]. Oxford University has also shown that mice lacking AMPA receptors exhibited deficits in short-term habituation, defined as a decrease in response to a frequently repeated stimulus[3]. The inability to regulate short-term habituation might be a cause of aberrant salience, defined as attribution of significance to irrelevant stimuli that drives psychotic symptoms[4]. In a study investigating the "aberrant salience" model schizophrenic patients at high risk of psychosis were more likely to attribute salience to irrelevant stimulus, and their bias was positively correlated with their positive symptoms[4]. In addition, fMRI of neuronal responses to relevant and irrelevant stimulus indicated alterations in the hippocampus, as well as in the striatum and subcortical dopamine system[4]. Additional information relevant to the research led by Bygrave worth noting is the term local field potential (LFP) which refers to the electrical field recorded in the extracellular space of brain tissue referenced against a recording made either inside or outside the tissue using electrodes, which capture the signals being transmitted between the neurons around the electrode[5]. The data collected by Bygrave and colleagues pointed to the AMPA receptors in the CA2/CA3 of the hippocampus as a target for treating positive psychotic symptoms in schizophrenic patients[1]. Further research must investigate possible road blocks to increasing GRIA1 protein levels in mice before it is considered as a treatment option for human subjects.

Simultaneous LFP recordings of the dorsal hippocampus and medial prefrontal cortex were collected while the control wildtype (WT) and the Grial1-deficient ($Gria1^{-/-}$) group performed hippocampus-dependent tasks assessing working memory and selective attention[1]. In addition, a rescue ($GLUA1_{CA2/3}$) group was created by reintroducing the AMPA receptor subunit GLUA1 in the CA2/CA3 of the $Gria1^{-/-}$ group[1]. The groups performed the T-maze, Y-maze, and a novelty-induced locomotion test[1]. The T-maze test measured exploratory behavior in rodents with central

nervous system disorders and is based on their willingness to explore novel environments[6]. Each trial consisted of a sample run in which mice were forced to leave the start arm and visit a goal arm, and a choice run in which mice could choose which arm to visit and were rewarded when they entered the previously unvisited arm. Each group was trained for seven days with 10 trials per day[1]. The Y-maze test measured rodents' willingness to explore novel environments[7]. Each test was conducted once per rodent, in the sample phase the mice could explore the start arm and one goal arm and in the test phase the mice could explore all three arms freely[1]. The novelty-induced locomotion test consisted of each mouse being able to freely explore plastic cages with saw dust for five minutes[1]. The data was processed in Matlab using the open-source Chronux Tool-box and analyzed with the statistical methods ANOVA or Tukey-HSD post hoc tests[1].

The results of the data collected by Bygrave and colleagues concluded that hippocampal-prefrontal coherence mediated working memory and selective attention at certain frequency ranges[1]. The T-maze test concluded that that the WT and GLUA1$_{CA2/3}$ performed significantly better than the Gria1$^{-/-}$ group which performed near chance levels[1]. Hippocampal-prefrontal beta/gamma coherence was significantly greater for the WT and GLUA1$_{CA2/3}$ group compared to the Gria1$^{-/-}$ group[1]. Hyperactivity of the Gria1$^{-/-}$ group was observed compared to the WT and GLUA1$_{CA2/3}$[4]. Constantly elevated levels of theta oscillations and hippocampal-prefrontal theta coherence in the Gria1$^{-/-}$ group compared to the WT and GLUA1$_{CA2/3}$ groups were recorded in novel environments[1]. The Y-maze test concluded that the WT and GLUA1$_{CA2/3}$ groups preferred the novel arm and the Gria1$^{-/-}$ group performed at chance levels[1]. Hippocampal-prefrontal theta coherence in the Gria1$^{-/-}$ group remained elevated after the hippocampal-prefrontal coherence in the WT and GLUA1$_{CA2/3}$ groups decreased in novel environments[1]. In addition, running speeds were not dependent on neither familiar or novel environments and did not predict coherence[1].

The results of the study imply a link between schizophrenia and lack of AMPA receptors in the hippocampus. The T-maze test measured the spatial working memory of the three mice groups. The control group and Gria1-deficient mice reintroduced with the AMPA receptor subunit GLUA1 in the CA2/CA3 of the hippocampus learned to visit the previously unvisited arm of the maze to obtain a food reward. The Gria1-deficient mice did not exhibit spatial working memory and visited each arm by chance during the test phase of each trial. The GLUA1$_{CA2/3}$ mice experienced significantly greater hippocampal-prefrontal beta/gamma coherence compared to the Gria1-deficient mice which indicated that spatial working memory was dependent on AMPA receptors in the CA2/CA3 of the hippocampus. The consistently elevated levels of theta oscillations in the dorsal hippocampus specific to the Gria1-deficient mice indicated a deficit in short-term habituation of attention which is common in patients with positive schizophrenic symptoms. The Spatial Novelty Preference (SPN) Y-maze test measured short-term habituation dependent on the hippocampus and the results indicated impaired preference between familiar and novel environments in the Gria1$^{-/-}$ mice compared to the WT and GLUA1$_{CA2/3}$ mice. In conclusion, the connection being regulated by the hippocampus was not controlled in the Gria1$^{-/-}$ mice, but control was restored when the AMPA receptor subunit GLUA1 was introduced in the CA2/CA3 of the hippocampus. The inability of the Grial1-deficient mice to reduce their response to stimulus they have been previously exposed to could be the result of dysfunctional regulation of selective attention through short-term habituation which may lead to aberrant salience[1]. As mentioned, aberrant salience is observed in schizophrenic patients[8]. It is important to study the mechanisms behind schizophrenia to develop treatments that can improve the quality of life for 3.2 million Americans and 1% of the population worldwide[9]. Schizophrenia is characterized by positive symptoms such as hallucinations and delusions, as well as negative symptoms such as lack of pleasure, trouble with speech, cognitive and thinking problems[10]. If the driving force of psychosis could potentially be treated by targeting AMPA receptors in the CA2/CA3 of the hippocampus then future research should build on the work of Bygrave and colleagues.

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