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Commentary

COMMENTARY

Hitting The Right Spot: NMDA Receptors in the Auditory Thalamus May Hold the Key to Understanding Schizophrenia

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Abstract

In this issue, Wang and colleagues solve an important puzzle in the understanding of schizophrenia. Previous work has linked N-methyl-D-aspartate (NMDA) receptor hypofunction to schizophrenia and shown that individuals with schizophrenia have a suppressed steady-state cortical response to 40-Hz repetitive auditory stimulation. However, systemic application of NMDA antagonists paradoxically increases this cortical response in rodents. Here, by specifically applying NMDA receptor blockade in the auditory thalamus while simultaneously measuring the acoustically driven response in 2 cortical regions, Wang and colleagues found the drop in the steady-state response that is seen in schizophrenia. These findings solve an important paradox in the field and suggest that specific thalamic neurochemical alterations may occur in the brain of individuals with schizophrenia. In addition, this work suggests that suppression of NMDA receptors in the thalamus may serve as a potential animal model for the disease.

Key Words: ASSR, schizophrenia, NMDA receptor, medial geniculate

Schizophrenia affects 1% of the world's population and devastates the social and emotional lives of individuals in the prime of their lives. Virtually every neurotransmitter has been implicated in the pathology of the disease. Recent hypotheses have been focused on hypofunction of the NMDA receptor in schizophrenia. For example, postmortem studies show that the expression level of NMDA receptors of individuals with schizophrenia is downregulated in many brain regions (Meador-Woodruff et al., 2003; Catts et al., 2016). NMDA receptor antagonism also elicits schizophrenia-like symptoms in healthy humans (Krystal et al., 1994) and exacerbates psychotic symptoms in individuals with schizophrenia (Malhotra et al., 1997). In addition, individuals with schizophrenia show diminished auditory sensory gating (Freedman et al., 1987), a phenomenon thought to involve inhibitory interactions between the auditory thalamus and the thalamic reticular nucleus. Could NMDA receptors in the auditory thalamus play a role in the pathophysiology of schizophrenia?

In the current issue of the *International Journal of Neuropsychopharmacology*, Wang and colleagues explore this question in an animal model and tackle a paradox that has existed in the literature. They examine the auditory steady-state response (ASSR) in mice and examine the role that N-methyl-D-aspartate (NMDA) receptors have on this response. The ASSR is a type of event-related potential that is entrained to temporally modulated auditory stimulation. It is maximally elicited by 40-Hz modulated stimuli in humans and may reflect the resonance frequency of the underlying neural circuits (Sivarao et al., 2016). Individuals with schizophrenia have a disturbance in such neural oscillatory activity (O'Donnell et al., 2013). A majority of studies on individuals with schizophrenia has revealed reductions of 40 Hz ASSR compared with healthy controls (reviewed by Thune et al., 2016). NMDA receptors play an important role in the 40-Hz oscillation in neural circuits (Carlén et al., 2012). To provide a translational model to study the pathogenesis of schizophrenia in animals, the effects of NMDA receptor antagonists on the

rodents have been studied. Surprisingly, most previous studies showed that the systemic application of NMDA receptor antagonists causes an increase in the 40-Hz ASSR in awake rodents (Vohs et al., 2012; Sullivan et al., 2015; Kozono et al., 2019), which contradicts the findings in individuals with schizophrenia.

To unravel this mystery, in the current issue Wang and colleagues for the first time examine the thalamic-specific effect of NMDA receptor antagonists on 40-Hz ASSR by conducting a tour de force experiment to locally administer NMDA antagonists to the medial geniculate body (MGB) of mice while measuring the ASSR in multiple cortical brain regions (Wang et al., 2020). To do this, they implanted electrodes in prefrontal cortex and auditory cortex (AC) to collect the local field potentials (LFP). They found that while both prefrontal cortex and AC gave a broad frequency range response to the onset of the 40-Hz click-train stimulus, only the AC had a narrowband steady oscillation response centered around 40 Hz after the onset response (the ASSR). Then they injected MK-801, an NMDA receptor antagonist, or vehicle locally to the MGB of mice and discovered that although the onset response was not altered by the local injection of MK-801, the mean trial power, which measured the power of LFP in spectral-temporal domains averaged across trials, and the phase-locking factor, which represented the phase synchronization across trials, of the 40-Hz steady response in the AC were significantly suppressed. They also studied the spiking activity of AC neurons by implanting multiple electrodes into the AC and found that the repetitive firing activity to the 40-Hz click-train stimulus of AC neurons was diminished by the local thalamic administration of MK-801, consistent with the LFP results. The above experiments provide novel evidence that the NMDA receptors in the MGB play a critical role in the generation of the ASSR in the AC and thus reconcile the paradox of the disparate impacts on the ASSR when systemic NMDA blockade is performed compared with what is seen in individuals with schizophrenia.

It is important to localize the administration of NMDA receptor antagonist to study the neural circuits of ASSR generation, because the NMDA receptors are present in many cell types throughout different brain regions. Although previous research shows that MK-801 preferentially decreases the firing rate of GABAergic in awake animals (Homayoun and Moghaddam, 2007), the GABAergic neurons in different brain regions (e.g., MGB, thalamic reticular nucleus, AC) can all participate in the generation of ASSR (O'Donnell et al., 2013; Thankachan et al., 2019). Thus, the authors' local administration of MK-801 in MGB and the following observation of the diminished ASSR in the AC suggests the specific facilitating role GABAergic projections to the MGB play in the generation of ASSR. This contradictory result compared with systemic administration of NMDA receptor antagonists implies that the GABAergic neurons in other regions may play an opposite role in the generation of ASSR or there is a more complicated mechanism that involves other neurons with NMDA receptors. Further studies on the specific roles of different cell types in different brain regions in the generation of ASSR are required.

Whether this local NMDA receptor hypofunction in MGB is also the specific mechanism inducing the ASSR deficits in individuals with schizophrenia is not yet clear. Several concerns need to be addressed. Postmortem studies in human individuals with schizophrenia find that the expression level of NMDA receptors is not only decreased in the thalamus (Meador-Woodruff et al., 2003) but also decreased in many other brain regions (Catts et al., 2016), indicating that the NMDA receptor hypofunction may not be restricted to MGB. Whether the MGB is the only region involved in ASSR among these regions or whether MGB NMDA receptor depression overshadows other regions should be studied in the future. Also, there are other ways established to attenuate the ASSR in rodents (e.g., inhibition of parvalbumin-positive neurons in the thalamic reticular nucleus) (Thankachan et al., 2019). Understanding which mechanism plays the central role in the suppression of ASSR in individuals with schizophrenia needs further and specific studies. The mice with local NMDA receptor hypofunction in MGB by local injection of NMDA receptor antagonists could be used as a translational model to study the pathogenesis of schizophrenia and develop the treatment of it; however, it is advised to test whether these mice present schizophrenia-relevant behaviors (Powell and Miyakawa, 2006), as some people show ASSR deficits without schizophrenia (O'Donnell et al., 2013).

Overall, Wang et al. (2020) resolve an important paradox by demonstrating the facilitating role of the neurons with NMDA receptors in MGB in the generation of ASSR. The lack of the activation of these neurons could possibly be the specific mechanism in the ASSR deficits in individuals with schizophrenia if some concerns could be addressed by further studies. Future studies will clarify interactions between the NMDA receptors on MGB neurons and thalamic reticular nucleus, another structure strongly implicated in schizophrenia and the formation of hallucinations (Ferrarelli and Tononi, 2017; Krol et al., 2018; Esmaeeli et al., 2019). Although the thalamic reticular nucleus is generally regarded as exerting inhibitory control over the MGB, recent work suggests that it may also serve an excitatory role (Willis et al., 2015; Brown et al., 2020). Thus, intrathalamic networks contain a wealth of complexity that may be disrupted in schizophrenia. Finally, focal blockade of NMDA receptors could also be a powerful translational model to study the pathogenesis of schizophrenia and develop the treatment of it if the model presents schizophrenia-relevant behavioral deficits.

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Statement of Interests

None.

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