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Ventral Hippocampus, Interneurons, and Schizophrenia: A New Understanding of the Pathophysiology of Schizophrenia and Its Implications for Treatment and Prevention

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Abstract
Dysfunction within the dopamine system has been the predominant hypothesized cause of schizophrenia for some time; however, there is little anatomical or postmortem evidence showing that the roots of this disorder are to be found within the dopaminergic neurons. Instead, the dopamine system appears to be dysregulated due to pathological influences from other structures. Recent postmortem and imaging studies have looked to the hippocampus as a potential site of this pathology. Our studies using a developmental animal model of schizophrenia found hyperactivity in the hippocampus likely drives the disruption in dopamine system function. This overactivity appears to be due to the functional loss of short axon interneurons that control the activity of the primary output neurons of the hippocampus. These data suggest that a more effective treatment of schizophrenia may be to normalize hippocampal function rather than block dopamine receptors. Moreover, given the high sensitivity of the hippocampus to stress-induced damage and the fact that stress is a risk factor for schizophrenia, controlling stress in the premorbid state may be an effective preventative measure to circumvent the transition to psychosis.

Keywords
dopamine, hippocampus, glutamate, schizophrenia, GABA, stress

Schizophrenia is a devastating disorder that affects more than 1% of the population, striking teenagers and young adults and causing severe impairment in cognitive and social functioning. For more than 40 years, the predominant model of schizophrenia has been based on dysfunctions of the dopamine system. This model was drawn from data showing that drugs that increase dopamine transmission tended to mimic psychosis in normal individuals and exacerbate psychosis in schizophrenia subjects; accordingly, the primary mode of treatment of schizophrenia was and continues to be the use of dopamine-receptor-blocking drugs (Grace, Bunney, Moore, & Todd, 1997). However, despite substantial efforts, a significant deficit in the dopamine system itself that was sufficient to cause such a widespread disruption of brain function has not been found. This led to the hypothesis that the disorder does not lie directly within the dopamine system but instead is due to an abnormal regulation of the dopamine system by other transmitters. The theory that function of the dopamine system is disrupted is reinforced by recent findings that, although baseline dopamine levels are not strongly elevated, amphetamine-induced dopamine release in humans (as determined by measuring the ability of amphetamine-induced release of dopamine to compete with the dopamine antagonist raclopride for dopamine receptors) is significantly greater in schizophrenia patients than in individuals without the disorder, and the increased release is proportional to the ability of the amphetamine to exacerbate psychosis (Laruelle & Abi-Dargham, 1999). Nonetheless, the source of this dysregulatory event has remained in dispute.

Glutamate, the Hippocampus, and Schizophrenia
Over the past decade or longer, interest in the role of glutamatergic systems in the pathophysiology of schizophrenia has grown. This interest has arisen because of several important findings. Although dopaminergic agents will exacerbate...
including thinning of limbic cortices with an increased cell packing density (as reported in schizophrenia patients), disruption of prepulse inhibition of startle reflex (a measure of sensory gating), disruption of latent inhibition, altered executive function, and hyper-responsivity to both phencyclidine and to amphetamine (Lodge & Grace, 2007; Moore, Jentsch, Ghajarian, Geyer, & Grace, 2006). Therefore, this model was consistent with schizophrenia in terms of both the genetic disruption and developmental origin and as validated by the anatomical disruptions, the behavioral alterations, and the pharmacological responses. This provided us with an effective animal model with which to examine the physiological properties of the neurons in this disorder.

**The Hippocampus Overdrives the Dopamine System in Schizophrenia**

As mentioned earlier, a consistent observation in schizophrenia patients is increased limbic hippocampal activity. Recordings in the ventral subiculum of MAM-treated rats (the rat limbic hippocampus that is analogous to the anterior hippocampal region in humans) revealed that the neurons were indeed hyperactive compared to controls. However, how this activity would translate into increased dopamine neuron responsiveness was unclear. Experiments found that activating the hippocampus subiculum using drugs produces a unique activity state of the dopamine system. The dopamine system has three activity states: The neurons can be firing or nonfiring (termed population activity), the neurons can be firing at different firing rates, or they can fire in a bursting or nonbursting pattern (Grace & Bunney, 1984). The burst pattern is considered to be the functionally relevant output of the dopamine neuron, since DA neurons will fire in bursts whenever an organism is presented with a behaviorally activating stimulus. Burst firing is driven by inputs from a brain stem region known as the pedunculopontine tegmentum—an area that is activated by various salient events. However, in order for a dopamine neuron to fire in bursts, it must first be spontaneously active; if it is not active, it cannot burst. Whether a neuron is active or not is dependent on its inhibitory input. The ventral pallidum is a brain region that has a potent and prominent GABAergic inhibitory influence over dopamine neuron firing; when it is active, dopamine neurons are in a nonfiring state (Grace, Floresco, Goto, & Lodge, 2007). When the hippocampus subiculum is activated using drugs, it drives firing in the ventral striatum, which in turn inhibits the ventral pallidum, thereby increasing the number of dopamine neurons firing spontaneously (Floresco, West, Ash, Moore, & Grace, 2003). Therefore, dopamine neuron activity is regulated by two processes: (a) a behaviorally salient signal that causes spontaneously firing dopamine neurons to burst fire; and (b) a modulatory “gain,” (i.e., how much the signal is amplified) whereby the hippocampus subiculum controls the number of dopamine neurons firing, and thereby controls the number of dopamine neurons that can be driven to burst fire by the behaviorally salient input from the pedunculopontine tegmentum (Lodge & Grace, 2006; Fig. 1).
What is the function of the ventral subiculum of the hippocampus, and how does the regulation of dopamine neuron gain contribute to this function? Various studies have shown that the subiculum plays a prominent role in context-dependent behaviors. The response that an organism makes in response to a stimulus depends greatly on the context in which the stimulus is presented. Thus, a stimulus (e.g., someone pointing at you) can have a very different interpretation in a rewarding context (e.g., games show) or a threatening context (a courtroom). Moreover, context dependency plays an important role in responses to stress and in relapse to drug abuse, both of which are context-dependent phenomena. The ability of the subiculum to regulate dopamine system responsivity would therefore be consistent with its involvement in context-dependent information processing. Thus, in a benign environment in which stimuli would not be predicted to have substantial salience, the subiculum would be less active, causing a smaller proportion of dopamine neurons to be spontaneously firing. If a stimulus is detected, the number of dopamine neurons that the brain stem pedunculopontine tegmentum will cause to burst fire would be smaller, and the dopamine response—and hence the attentional state—would be minimal. However, if the individual is in a highly threatening environment in which great attention must be directed toward any event, or alternately in a highly rewarding environment in which stimuli are likely to signal a strong reward (e.g., a casino or hunting for food), the hippocampal subiculum maintains the DA system in a highly active state. Now, when a novel stimulus is encountered, the system is positioned to assign a high level of behavioral salience and is prepared to respond appropriately.

**Fig. 1.** Role of the hippocampus subiculum in controlling the relative amplitude of the dopamine (DA) response to a stimulus, depending on the environmental context. In a benign environment (a)—one in which a substantial threatening stimulus is unlikely to be encountered or in which the opportunity for a substantial reward is minimal—the hippocampus subiculum maintains a low level of DA neuron activation; that is, a small percentage of DA neurons are active. As a result, when a novel stimulus is encountered, the signal from the pedunculopontine can only signal an event (i.e., generate a burst of spikes) from the small number of DA neurons that are already active. As a result, the stimulus does not have a strong attribution of salience and does not require a vigorous response. But if the individual is in an environment that is highly threatening (b)—one in which failing to respond could have lethal consequences—or alternately is in an environment in which stimuli are likely to signal a strong reward (e.g., a casino or hunting for food), the hippocampal subiculum maintains the DA system in a highly active state. Now, when a novel stimulus is encountered, the system is positioned to assign a high level of behavioral salience and is prepared to respond appropriately.
What is the state of the dopamine system in the MAM model of schizophrenia? Recordings made in the dopamine neuron group reveal that, just as in the case of pharmacological activation of the ventral subiculum, there are more than twice as many dopamine neurons firing in the MAM-treated rat as in the control animal (Lodge & Grace, 2007). Therefore, the hyperactive ventral subiculum would cause the dopamine system to be in a hyper-responsive state (Fig. 2). Consequently, any stimulus that arrives, whether it is strongly salient or even nonsalient, could drive the dopamine system maximally. This would cause the individual to attend to all stimuli indiscriminately, with little ability to select between important and irrelevant stimuli, and thus with all events demanding maximal attention. Because the dopamine system is tagging all stimuli as highly relevant and of immediate overriding importance, the individual could be expected to interpret the stimulus in a manner that is consistent with this tagging. Such a condition could lead the patient to attribute to the signal excessive motivational salience (i.e., level of importance as it relates to the individual’s well-being, which is suggested by Kapur to lead to psychosis (Kapur, 2003).

Therefore, hyperactivity in the limbic hippocampal regions could lead to the aberrant overdrive of the dopamine system, causing the individual to inappropriately attribute maximal salience to nonrelevant situations and events. But what is the source of this hyperactivity? Postmortem studies in humans have shown that the hippocampus and the prefrontal cortex are missing a critical neuronal component, the inhibitory interneurons that contain the peptide parvalbumin (Zhang & Reynolds, 2002). Parvalbumin interneurons contain and release the inhibitory neurotransmitter gamma aminobutyric acid (GABA) that inhibits, or limits, the activity of pyramidal neurons, the neurons that provide the output of the hippocampus and prefrontal cortex. This class of parvalbumin interneurons is essential for the normal functioning of cortical structures; if these neurons are damaged, rhythmic activity in cortical structures is disrupted. In particular, there is a loss of evoked gamma rhythms, electroencephalogram rhythms measured over the cortex that are associated with stimulus recognition and higher cognitive functions. Gamma rhythms are known to be disrupted in schizophrenia. Indeed, our studies revealed that MAM rats also show a selective loss of parvalbumin-containing interneurons in both the hippocampus and the prefrontal cortex (Lodge, Behrens, & Grace, 2009). As a consequence of this loss, these brain regions in the MAM rats also show a disrupted gamma rhythm response to conditioned stimuli: A tone paired with a foot shock will evoke gamma rhythms in the ventral hippocampus and prefrontal cortex in normal rats, but in the MAM-treated rats the same conditioned tone fails to evoke gamma rhythms in the regions in which a loss of parvalbumin interneurons was found. This interneuron component is clearly critical for the normal rhythmic function of these circuits; if these neurons are damaged, then the normal gated rhythmic activity may be replaced by a nonspecific higher-frequency output, disrupting cognitive functions mediated by these regions and overdriving the dopamine system.
Stress-Induced Hippocampal Damage: Insights Into Potential Methods for Schizophrenia Prevention

Among the risk factors that can lead to a transition to schizophrenia is stress. Exposure to stress is known to lead to relapse, and environmental or social stressors can be a precipitating factor in schizophrenia (Murray & Fearon, 1999). Our studies show that stress will cause an activation of the hippocampus and an overdrive of the dopamine system (Valenti & Grace, 2008). Thus, in a susceptible individual, stressors may reveal an underlying premorbid psychotic state. But more than this, stress in itself may lead to the pathophysiological changes in the brain that engender a psychotic break. Indeed, studies have shown a strong link between stress and hippocampal pathology, in that stressors are known to precipitate damage in the hippocampus. We have shown that the prefrontal cortex is an important area regulating stress responses. Activation of the prefrontal cortex will attenuate stress responses via inhibition of the amygdala (Rosenkranz & Grace, 2002), which we propose will enable an individual to regulate responses to stressors. However, if the prefrontal cortex is not sufficiently engaged, as may occur in schizophrenia, then the stress response would be unregulated. This could lead to a cascade of events whereby an underlying prefrontal dysfunction produces a pathologically large stress response to stimuli, which then could lead to hippocampal damage. The hippocampal damage would, in turn, lead to dysregulation of the dopamine system, which in itself would exacerbate the stressful condition (Thompson, Pogue-Geile, & Grace, 2004). It may be that the hippocampal damage caused by unregulated stressors is a primary pathophysiological factor leading to disruption of hippocampal interneuron function and consequently overdrive of the dopamine system. Indeed, studies by Johnstone (Johnstone, Lawrie, & Cosway, 2002) show that, among children at risk for schizophrenia, those showing the highest stress responses tended to be the ones that transitioned to schizophrenia. If this is indeed the case, then it is possible that transition to psychosis in susceptible individuals could be diminished by controlling this proposed unregulated stress response. This was tested in our animal model. Preliminary data show that, in rats that had been treated prenatally with MAM, administration of the anti-anxiety drug diazepam around puberty actually prevented the hyperdopaminergic state in adult animals (Fox & Grace, 2009).

Summary

These data provide a pathophysiological basis for schizophrenia in humans: hippocampal damage leading to dysregulation of the dopamine system. In addition, it provides a potential explanation for hippocampal damage arising from a pre-existing pathology within the prefrontal cortex that may predispose an individual to stress-induced hippocampal damage. An extension of these studies would suggest that a more effective treatment for schizophrenia than the current dopamine-blocking antipsychotic drugs would be one that involves restoring inhibitory function within the limbic hippocampus. On the other hand, if susceptible individuals can be identified—for example, based on abnormal stress responses in the genetically at-risk population—we may be able to circumvent the transition to schizophrenia merely by treating the stress condition that is already present (Thompson et al., 2004).

Recommended Reading


Grace, A.A., Floresco, S.B., Goto, Y., & Lodge, D.J. (2007). (See References). This paper provides an overview of the gain model and how it is related to regulation of behavior.

Grace, A.A., & Sesack, S. (2010). The cortico-basal ganglia reward network: Microcircuitry. Neuropsychopharmacology, 35, 4–26. This paper provides an overview of the circuitry of the cortex and basal ganglia as they relate to reward and affect, and how they affect behavior.


Declaration of Conflicting Interests

The author declared that he had no conflicts of interest with respect to his authorship or the publication of this article.

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