Commentary

Biological Psychiatry

Dopamine System Dysregulation and the Pathophysiology of Schizophrenia: Insights From the Methylazoxymethanol Acetate Model

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Data from numerous studies have strongly implicated the dopamine (DA) system in the pathophysiology of schizophrenia. The data are particularly robust for the positive or the psychotic symptoms of schizophrenia, which can be mimicked by DA agonists and attenuated by D_2 antagonist antipsychotic drugs. Nonetheless, there is little evidence for a major dysfunction within the DA system itself; instead, current research has focused on a disruption in the regulation of the DA system. One region in particular that has shown correlations with DA dysfunction is the limbic portion of the hippocampus, which comprises the ventralmost segment in rats analogous to the anterior aspect in humans. Thus, studies in patients with schizophrenia have shown hyperactivity in the hippocampus that correlates with psychosis as well as a loss of parvalbumin gamma-aminobutyric acid–ergic (GABAergic) inhibitory neurons (1). To examine the pathophysiology of schizophrenia, we employed a developmental disruption model that uses the mitotoxin methylazoxymethanol acetate (MAM). This drug is administered to pregnant rats at gestational day 17 to mimic the second trimester in humans, during which insults have a higher impact on inducing schizophrenia births. The offspring are then examined peripubertally for developmental changes and as adults to test for dysfunctions that correspond to schizophrenia in humans.

The adult offspring of MAM-treated rats display many characteristics consistent with schizophrenia (2,3), including neuroanatomic changes (thinning of limbic cortices with an increase in cell packing density, loss of parvalbumin interneurons), behavioral deficits (prepulse inhibition of startle, reversal learning, extradimensional shift, latent inhibition, social interaction), and pharmacologic responses (hyperresponsivity to phencyclidine, increased locomotion to amphetamine). Furthermore, as in humans, there is hyperactivity in the ventral hippocampus (vHipp) and a disruption of rhythmic activity including delta and gamma rhythms (3). There was also a substantial increase in DA neuron population activity.

In anesthetized and awake rats, DA neurons exhibit several activity states that are regulated by different systems and differentially affect system function (Figure 1). In the basal state, DA neurons discharge in a slow, irregular tonic firing pattern. However, if the organism is exposed to a behaviorally salient stimulus, DA neurons transition to a rapid burst-firing mode. Thus, burst firing is considered to be the behaviorally relevant phasic response to stimuli. Burst firing is driven by a glutamatergic input arising primarily from the brainstem pedunculopontine tegmentum (PPTg) acting on *N*-methyl-D-aspartate (NMDA) receptors (1). However, for glutamate to activate NMDA receptors, the neurons must be in a depolarized, spontaneously firing state; otherwise, there is a magnesium block of the NMDA channel. Therefore, only neurons that are firing are capable of transitioning to burst firing. The number of DA neurons firing (i.e., population activity) is controlled by a potent GABAergic input from the ventral pallidum (VP) that holds a subset of neurons in a nonfiring state. The PPTg drives the phasic burst firing, but the VP controls the number of DA neurons that can be driven to burst firing or, in essence, the level of amplification of the phasic signal.

The VP itself is potently modulated by a circuit originating in the vHipp to the ventral striatum. When the vHipp is activated, it drives the ventral striatum, inhibiting the VP and releasing the DA neurons from inhibition to increase population activity. The vHipp itself has been associated with context dependency, or the ability to adjust behavioral responses depending on the context or setting. Therefore, the gain of the DA system depends on the behavioral context: the more DA neurons firing, the greater the behavioral activation (1). In a benign context, the vHipp drives a low DA population activity; when a behaviorally salient stimulus activates the PPTg, only a few DA neurons transition to burst firing, and the phasic signal is low in amplitude. However, in a highly threatening context, the vHipp drives large increases in DA population activity such that the same stimulus causing the same PPTg activation now causes a massive DA phasic response to effectively deal with the potentially threatening event.

In MAM rats, there is a near doubling in the number of DA neurons spontaneously firing compared with control rats; this occurs in the lateral ventral tegmental area that projects to the associative striatum (4) and can be reversed by inactivating the vHipp. Moreover, vHipp inactivation also normalizes the increased locomotor response to amphetamine in MAM rats. The increase in DA neuron population activity is consistent with the increased fluorodopa uptake observed in patients with schizophrenia (5); increased fluorodopa uptake indicates more DA terminals are active and is consistent with more DA neurons firing. Therefore, in MAM rats or in patients with schizophrenia, any stimulus whether it is salient or not will cause a massive DA system response, causing the individual to be unable to selectively filter between threatening or neutral stimuli. This increased DA system responsivity is also consistent with studies showing increased amphetamine-induced DA release in patients with schizophrenia that correlates with worsening of psychosis (6).

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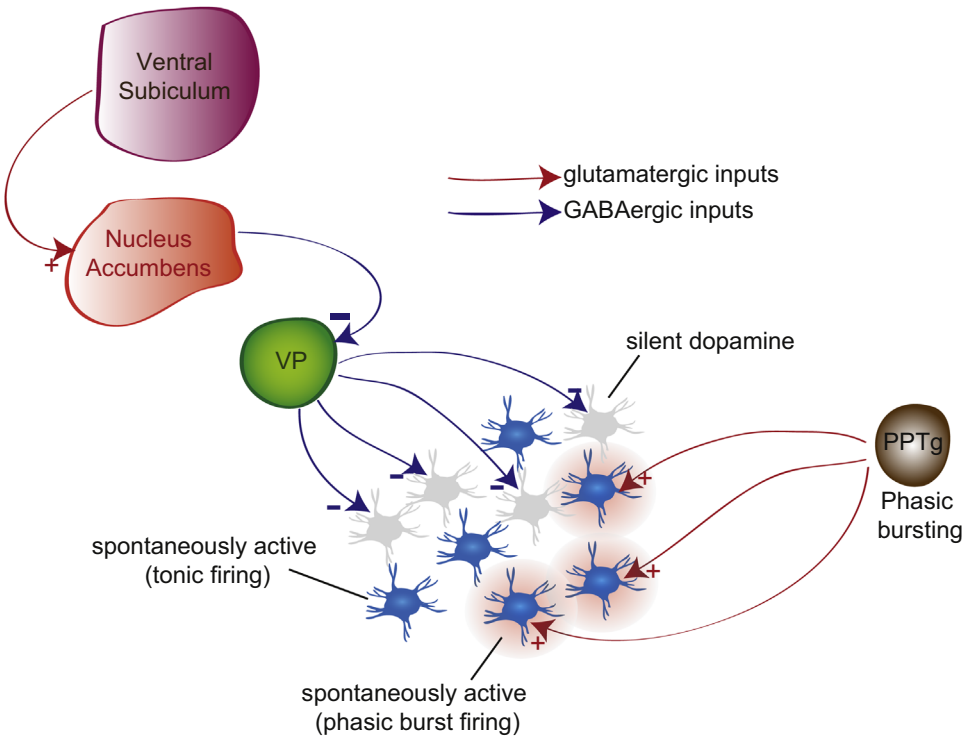

Figure 1. Dopamine neurons exist in distinct states of activity: baseline tonic population activity (i.e., proportion firing spontaneously) and rapid, salience-driven phasic burst firing. In normal rats, approximately one half are firing spontaneously, with the other half in an inhibited, nonfiring state. This inhibition is maintained by a potent gamma-aminobutyric acid–ergic (GABAergic) inhibitory input from the ventral pallidum (VP). This state is regulated by input from the hippocampus ventral subiculum. Activation of the subiculum excites the nucleus accumbens, which inhibits the VP to release dopamine neurons from inhibition. The number of dopamine neurons that are active is an important variable, in that it sets the amplitude of the rapid, burst firing–mediated phasic dopamine response driven by the pedunculopontine tegmentum (PPTg). Because only spontaneously firing dopamine neurons can be driven to burst fire, changing the number of neurons that are active affects the amplitude of the phasic dopamine response.

Why is the vHipp hyperactive in patients with schizophrenia and in MAM rats? A robust finding in schizophrenia brains is a loss of parvalbumin-containing inhibitory GABAergic neurons in the prefrontal cortex and the hippocampus, which correlates in both patients with schizophrenia and MAM rats with a loss of parvalbumin-dependent evoked gamma rhythmic activity. This loss of parvalbumin occurs early in development, with neuronal loss in the hippocampus emerging in young adults (7). Therefore, we propose that the loss of parvalbumin inhibition in the vHipp drives the increased vHipp activity, which increases DA neuron responsivity, leading to psychosis (Figure 2). Current treatments for schizophrenia depend on reversing the overstimulation of DA receptors in the striatum using DA antagonists. Our studies show that DA receptor blockade by antipsychotic drugs leads to an overdrive of the DA system in MAM rats, decreasing DA neuron population activity via depolarization block–induced inactivation of firing. Given that depolarization block depends on a baseline hyperactive state, this could account for why antipsychotic drugs show the most rapid onset in the most psychotic patients, presumably because of the higher baseline population activity. However, this approach is not restoring the system to normal; it is instead acting at a site that we believe is at least five synapses downstream from the deficit in the hippocampus. A more effective approach would be to restore inhibition in the hippocampus. For this, we used a gamma-aminobutyric acid A alpha 5 positive allosteric modulator because the alpha 5 subunit is selectively concentrated in the hippocampus. We found that this drug selectively restored normal hippocampal firing, restored normal DA neuron population activity, and normalized the behavioral response to amphetamine in MAM rats (8). However, other drugs that should work on this circuit have been tested clinically and have failed to show efficacy despite encouraging preclinical results. However, there is an important difference between the preclinical and clinical trials; in the clinic, patients have already been exposed to many years of antipsychotic treatment and are withdrawn from treatment for only 1 week before testing the novel compound. We found that pretreating the MAM rats with haloperidol for only 3 weeks and withdrawing them for 1 week completely prevented the actions of our novel compound (9). Therefore, we propose that pre-exposure to an antipsychotic drug changes the DA system from a hippocampal-overdriven DA system to a postsynaptic supersensitive DA system, such that on withdrawal only another DA antagonist would be effective. This situation demonstrates the need to select patient populations carefully when evaluating drugs with novel actions.

Although these studies show a potentially more effective therapeutic target, a better approach would be to prevent the transition to schizophrenia in susceptible individuals. A major risk factor in schizophrenia is early life stress. Studies have shown not only that early life stress predisposes one to schizophrenia, but also that children at risk for schizophrenia who show higher stress responsivity are more likely to transition to schizophrenia. We found that MAM rats examined peripubertally before parvalbumin neuron loss showed higher anxiety and stress responsivity compared with control rats. Therefore, we tested whether attenuating stress at this critical period would impact adult MAM rats. We found that anxiolytic doses of diazepam administered for 10 days peripubertally