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Dopamine in the thalamus: a hotbed for psychosis?

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Nearly twenty years ago an article in *Biological Psychiatry* described unusually high levels of dopamine in the thalamus of individuals with schizophrenia (1). I had just started my graduate research work in the laboratory of Ralph Adams where this work was being performed. Adams was convinced that thalamus is critical to the pathophysiology of schizophrenia and where maladaptive sensory processing that leads to thought disorder and other positive symptoms occurs. The postmortem wing of the lab was busy measuring norepinephrine turnover as that was believed to be the key neuromodulator that regulated thalamic function. The dopamine projection to the thalamus was thought to be non-existent or scarce at the best and any dopamine found in thalamic tissue was assumed to be a precursor for norepinephrine. The high levels of dopamine in the thalamus of patients which appeared to have normal dopamine levels in striatal regions was therefore considered “peculiar” but quite interesting in the context of theories related to sensory processing dysfunction in schizophrenia and regulation of cortical oscillatory activity (2). Subsequent work showed that the dopamine projection to the thalamus is not negligible and a paper in this issue of *Biological Psychiatry* incorporates aberrant thalamic dopamine into a systems oriented model of psychosis that integrates NMDA receptor deficiency and dopamine hyperactivity hypotheses of schizophrenia (3).

The model proposed by Lisman et al (3) builds on the so called NMDA deficiency hypothesis of schizophrenia. The use of NMDA antagonists as an animal model of schizophrenia has gained wide acceptance for three primary reasons: (I) the treatment has face validity; a single dose of these antagonists is sufficient to transiently produce several symptoms of schizophrenia in healthy individuals(4,5); (II) it is easy to implement in animals in that a single dose of these compounds produces a whole host of aberrant behavioral effects in animals(6); and (III) a recent clinical trial suggested that it may be a useful model for discovery and characterization of novel non-monoaminergic antipsychotic drugs (7). But application of this model to pathophysiological hypotheses that have the potential to enhance our mechanistic understanding of the etiology of schizophrenia has been somewhat limited. Specifically, the relative lack of concrete findings at genetic and postmortem levels showing structural or functional abnormalities in NMDA receptors suggest that the pro-psychotic impact of NMDA antagonists may be primarily due to downstream effects that mimic an abnormal state at the systems levels that occurs in schizophrenia, as opposed to an NMDA receptor hypofunction *per se*. The NMDA antagonists that cause schizophrenia-like behaviors are, so far, non-competitive channel blockers meaning that they specifically block open channels, i.e. NMDA receptors, where

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the ion channel has been already opened by endogenous glutamate. Thus, when applied systemically, these antagonists selectively inhibit “active” glutamatergic pathways. The focus on these active pathways in the context of schizophrenia has been primarily in the prefrontal cortex and to some extent the hippocampus where these antagonists produce overt effects on cell activity (8,9) and disrupt behaviors such as working and spatial memory that are traditionally associated with these cortical regions. But as correctly pointed out by Lisman et al., some of the global effects of NMDA receptor antagonists can be mimicked by local microinjection of the antagonist into the thalamus and not cortical areas (10) suggesting that the thalamus is critical for the behavioral effects of these compounds. Given this, Lisman et al (3) emphasizes an important and translationally relevant physiological mechanism which is that thalamic activity is critical for generation of delta frequency oscillations in the cortex. This is important because there is enhanced EEG delta power in schizophrenia (11). Both NMDA and dopamine receptors in the thalamus, in particular the nucleus reticularis of the thalamus, influence delta oscillation generation (12). Inhibition of NMDA receptors increases delta frequency bursting in the thalamus. Dopamine has a similar influence and synergistically enhances the delta frequency bursting elicited by NMDA antagonists whereas as dopamine D2 antagonists block this effect.

The thalamus extensively projects to all cortical regions including the hippocampus. These projections are primarily excitatory (glutamatergic) and often reciprocated. Lisman et al (3) propose that a positive feedback in a thalamus-hippocampus-VTA circuit may act as a trigger for psychosis in predisposed individuals where a state of NMDA receptor deficiency is combined with a transient increase in dopamine release. This combination produces rapid bursting of thalamic cells and associated networks and throws this loop into the positive feedback eliciting psychosis. The strengths of this model are that (1) it utilizes a systems level approach to explain a real physiological finding in schizophrenia related to delta frequency oscillations and (2) it is not dependent on a single pathology because changes in NMDA receptor or other glutamatergic components (e.g. AMPA receptor trafficking, glutamate transport systems) that regulate the dynamics of the NMDA channel, as well as an aberrant dopamine system could alone or in concert impact the function of this loop. In relation to dopamine, Lisman et al (3) suggest that stress activation of the dopamine system is critical for the excess dopamine needed to put thalamic cells in a bursting mode and activate the thalamus-hippocampus-VTA loop. Indeed stress is critical for manifestation or exacerbation of psychosis. However, despite the belief that stress is a potent activator of the dopamine system, all salient conditions, appetitive or aversive as well as conditions of high cognitive demand increase dopamine (13) as much if not more robustly than stress (14). Dopamine cells in the VTA are highly responsive to most forms of sensory stimulations but are generally inhibited by stressful conditions (15). A key point about dopamine cells in the VTA, however, is that they are highly plastic and increase their pattern of response based on learned associations. This characteristic of dopamine cells may be more relevant to the current model than the presumed stress reactivity of the dopamine system. As shown in figure 1, a tone presented to an animal as a novel stimulus produces a short lasting phasic increase in the activity of dopamine cells in the VTA. After the animal learns that the same tone is accompanied by reward delivery, the same tone produces a large response in the dopamine neuron. After this contingency is removed, the response to the tone is reduced. This pattern of plasticity is most likely critical for the proper functioning of the dopamine system in processing all forms of salient internal or external inputs. An irregular pattern of plasticity and excess response of the dopamine system to salient input could be a more plausible mechanism by which excess dopamine is generated to activate the proposed feedback loop. The dopamine system undergoes substantial remodeling during adolescence and early adulthood which could influence its pattern of plasticity to learned associations (16), consistent with the onset of psychotic episodes in schizophrenia occurring during this developmental period. In the context of stress, the role of the other components of this

circuit should not be discounted. Hippocampus is one of the most “stress-sensitive” regions of the brain (17). Stress enhances glutamate release in this region similar to NMDA antagonists (18) and therefore could increase the activity of hippocampal CA1 neurons which could facilitate the generation of the positive feedback loop.

In sum, Lisman et al propose a thought provoking but straightforward model that takes into account some clinical features of schizophrenia and consolidates NMDA and dopamine hypotheses in relation to the psychotic breaks of the disease. The model will hopefully generate greater interest in including thalamus as a key component of the pathophysiology of the disease. It is the region where all sensory information except olfaction pass through before getting to the cerebral cortex and hippocampus. It is also a critical region for the “phasic recycling” of internally generated activity (19). It is exquisitely sensitive to dopamine and provides the major source of excitatory input to the neocortex and the hippocampus. Its incorporation into a physiologically relevant and symptoms specific model for schizophrenia, a disease which at its core involves sensory processing dysfunction, is a welcome addition to the field.

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Figure 1.

(A) Recording from the ventral tegmental area (VTA) of behaving rats from neurons that have characteristic waveform of dopamine neurons (B) shows phasic activation to a novel tone (C) that progressively gets larger (D) once the animal learns to associate this tone to an appetitive outcome, in this case sugar pellet delivery but the response to the same tone gets smaller (E) once the contingencies are changed and the tone no longer predicts reward.