COMMENTARY

Implications of Striatal Dopamine Signalling for Schizophrenia

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ABSTRACT

Our understanding of striatal dopamine function has come a long way since the inception of the dopamine hypothesis of schizophrenia. Advances in this field have largely been contributed by the technique of optogenetics and have in turn helped provide a neural basis for the motivational-salience theory of psychosis. Studies of striatal dopamine function have proven to be a promising area of research with important implications for our understanding of schizophrenia and its treatment.

RÉSUMÉ

Notre compréhension de la fonction striatale de la dopamine a beaucoup avancée depuis le début de l'hypothèse de la dopamine dans la schizophrénie. Les avancées dans ce domaine ont été largement apportées par la technique de l'optogénétique et ont, à leur tour, contribué à fournir une base neurale pour la théorie de la motivation-salience de la psychose. Les études sur la fonction striatale de la dopamine se sont révélées être un domaine de recherche prometteur avec des implications importantes pour notre compréhension de la schizophrénie et de son traitement.

INTRODUCTION

Schizophrenia is a chronic and debilitating psychotic disorder, with a prevalence approaching 1% internationally. It is among the most disabling and economically disastrous medical disorders and is ranked by the World Health Organization as one of the top 10 illnesses contributing to global burden of disease (1). Dopamine (DA) dysfunction is central to the underlying pathophysiology of schizophrenia. Excessive DA signalling in the mesolimbic pathway, which projects from the ventral tegmental area in the midbrain to the ventral striatum, is thought to mediate the positive symptoms of schizophrenia, including hallucinations and delusions. Conversely, reduced DA signalling in the mesocortical pathway, which projects from the ventral tegmental area to the prefrontal cortex, is thought to mediate the negative and cognitive symptoms of schizophrenia, including poverty of speech, apathy and inattention to social or cognitive input (2).

D2 receptors are G-protein coupled receptors, which bind DA, and are implicated in several neuropsychiatric disorders, including schizophrenia. Antipsychotic medications exert their effect via D2 receptor antagonism, thereby reducing the positive symptoms of schizophrenia. Thus far, antipsychotics have remained limited in their ability to target the negative and cognitive symptoms of schizophrenia.

Recent studies have demonstrated significant variation in DA signalling across the striatum. The striatum is a subcortical structure in the midbrain that modulates neuronal input to the basal ganglia. It consists of the dorsal (i.e., caudate, putamen) and ventral (i.e., nucleus accumbens) striatum and is implicated in regulating motor behaviours as well as responding to rewarding and aversive stimuli (3). In schizophrenia, DA release has been shown to be increased in the dorsal striatum, where it is associated with positive symptoms, and reduced in the ventral striatum, where it is associated with negative symptoms (3). Optogenetics is a biological technique, which uses light to control neurons that have been genetically modified to express light-sensitive ion channels. Optogenetics has enabled the selective targeting of striatal DA neurons to enable functional connectivity analyses, which has allowed for the study of these neurons at a synaptic level (2). Importantly, optogenetic studies of striatal DA function have shown promise in advancing our understanding of the pathophysiology and treatment of schizophrenia.

PRE-SYNAPTIC REGULATION OF DOPAMINE SIGNALLING

The striatum is divided broadly into associative, sensorimotor and limbic domains, based on the source of excitatory input (4). There is significant variation in DA signalling across these three domains, based on the location of the neuron within the striatum and the specific post-synaptic target. Pre-synaptic regulation of excitatory input has been shown to modulate DA neuron signalling (5). This modulation of synaptic transmission has long-term effects on motivational salience, vigor and social behaviour (6). These behavioural effects, particularly those involving motivational salience, have important implications for schizophrenia, which are discussed later in the text. Modulation of DA signalling is, in part, facilitated by co-transmission with glutamate and GABA. Our current model of schizophrenia involves reduced cortical DA release, leading to increased activity of glutamatergic neurons and increased striatal DA synthesis and release (7). There are a number of genetic risk factors that act on these upstream pathways, particularly the glutamatergic system. Impaired glutamatergic regulation of midbrain DA neurons may make them more vulnerable to acute psychosocial stressors (7). This is in keeping with the diathesis-stress model, which posits an interaction between inherent genetic vulnerability and environmental stressors in the etiology of schizophrenia.

Co-transmission of glutamate with DA is thought to mediate DA neuron fast actions. This is supported by the finding that monosynaptic DA neuron excitatory connections depend on the expression of vesicular glutamate transporter 2 (VGLUT-2) (8). Most DA neurons also co-release GABA, which is loaded into vesicles by vesicular monoamine transporter 2 (VMAT-2) (9). Co-transmission with glutamate and GABA greatly increases the diversity of DA-neuron synaptic signalling. These co-transmitters can either excite or inhibit post-synaptic cholinergic interneurons and spiny projection neurons. Spiny projection neurons are the primary cell type in the striatum, and release GABA at their synaptic terminals (10). Cholinergic interneurons are another cell type in the striatum, which are implicated in reward-predicting stimuli and may play a role in learning (10). Co-transmission with glutamate and GABA plays an important role in encoding phasic firing patterns (i.e., a transient response to a stimulus followed by accommodation) throughout the striatum (10).

Imaging studies have identified pre-synaptic striatal DA dysfunction during the prodrome (i.e., early phase) of schizophrenia, suggesting that it is associated with the development of psychosis (7). DA release is mediated by vesicular loading, a process that demonstrates diversity across the striatum. Vesicular loading is performed by VMAT-2 and is regulated by VGLUT-2 (11). VGLUT-2, which mediates glutamate co-transmission, also mediates vesicular DA release via vesicular synergy (12). Vesicular synergy refers to a process by which packaging, and release of DA is enhanced by co-transmission with glutamate. Vesicular synergy in VGLUT-2-expressing DA neurons has been implicated in reward processing (8). The role of vesicular synergy in DA release is believed to be most prevalent in the nucleus accumbens, which is an important part of the brain's reward circuitry (10). Reduced reward-pathway signalling could be implicated in some

of the negative symptoms of schizophrenia, including avolition (i.e., lack of motivation) and anhedonia (i.e., inability to feel pleasure).

DOPAMINE NEURON FIRING

Dysfunctional DA release in schizophrenia can also be attributed to abnormalities in DA neuron firing. This firing depends on both intrinsic membrane properties as well as synaptic inputs (13). There is significant variation in both membrane conductance and synaptic input throughout the striatum. In mouse models, DA neurons alternate between tonic and phasic firing, and this is determined by synaptic inputs (10). Tonic firing refers to a sustained neuronal response, which activates during the course of a stimulus. Whereas phasic firing refers to a transient response with one or several action potentials at the onset of a stimulus, followed by accommodation. The regularity and frequency of pacemaker firing (i.e., firing in the absence of synaptic input) is controlled by differences in membrane conductance (14). The slow membrane potential oscillations that drive pacemaker firing differ between substantia nigra and ventral tegmental area neurons (13). The substantia nigra projects to the dorsal striatum via the nigrostriatal pathway and the ventral tegmental area projects to the ventral striatum via the mesolimbic pathway. The variations in slow membrane potential oscillations between these two pathways produce complex patterns of burst firing (i.e., intermittent discharge of rapid action-potential sequences) throughout the striatum. There is a gradient of decreasing burst firing from the ventral tegmental area to the lateral substantia nigra (15). Small-conductance calcium-activated potassium channels are a family of calcium-activated potassium channels that generate slow membrane potential oscillations in DA neurons (16). The expression of these channels follows a gradient that closely matches the gradient of burst firing frequency (16). These channels may therefore regulate the excitability gradient observed across striatal DA neurons. It is possible that differences in tonic and phasic DA release in the ventral and dorsal striatum contribute to the increased DA transmission in the associative striatum (10).

Pre-synaptic acetylcholine (ACh) receptors also contribute to regional variations in DA transmission across the striatum and may be implicated in schizophrenia (17). These nicotinic receptors mediate the balance between tonic and phasic firing of DA neurons (18). Enhanced DA neuron burst firing in the dorsal striatum may draw attention to less salient cues in individuals with schizophrenia (19). Saliency is defined as the extent to which an environmental cue stands out from others. Identifying salient environmental cues is a key component of attentional awareness, by focusing cognitive resources on the most pertinent sensory information. Inability to distinguish between salient and non-salient environmental cues has been proposed as a mechanism underlying psychosis. Low-level phasic DA release in the ventral striatum may also contribute to disturbances in salience signals (19). This could explain the inattention to social and cognitive input that underlies the negative symptoms of schizophrenia. Activation of nicotinic ACh receptors on DA neuron terminals has been shown to increase DA release by a single action potential and limit DA release by subsequent action potentials (20). Disruptions in these patterns of DA release could interfere with the appropriate assignment of salience to various environmental cues.

ROLE OF DOPAMINE SIGNALLING IN REWARD PROCESSING & MOTIVATIONAL SALIENCE

Research has demonstrated that there is extensive variation in DA signalling throughout the striatum. A theoretical framework that relates abnormal DA signalling to psychosis must be developed if the implications of this research are to be understood. The role of DA in reward processing has often been linked to psychosis. The firing of midbrain DA neurons is known to be associated with reward prediction (19). In this process, the DA system is activated when novel rewards are encountered or when well learned associations are broken (21). This information is encoded via burst firing of DA neurons in the limbic regions and subsequent phasic release of DA (21).

The DA system is also involved in long-term regulation of motivational salience. Motivational salience is the process by which reward-associated stimuli become conspicuous and guide goal-directed behaviour (19). Abnormal DA-mediated motivational salience has been hypothesized as a mechanism underlying psychosis (19). Typically, DA mediates the experience of novel stimuli and the appropriate development of motivational salience. In schizophrenia, the DA system is dysregulated, and DA is released regardless of the environmental context.

Therefore, in psychosis, the DA system drives an abnormal sense of novelty and inappropriate assignment of salience to internal and external stimuli (19). This theoretical framework can be used to explain the positive symptoms of schizophrenia. Delusions can be thought of as cognitive explanations used to understand experiences which are inappropriately assigned novelty or salience (19). In the case of thought insertion (i.e., the feeling that one's thoughts are not their own), individuals with schizophrenia may attempt to explain the abnormal salience of their thoughts by ascribing them to an outside source (22). Hallucinations are thought to result from the abnormal salience of internal stimuli, such as language or memories (23).

The abnormal-salience model can also be used to explain the mechanism of antipsychotic action. By blocking DA transmission, antipsychotics may be able to reduce the abnormal salience of the individual's experiences (19). By reducing salience, individuals with schizophrenia are gradually able to extinguish the cognitive frameworks that they developed to make sense of their experiences. However, the salience of all experiences is diminished, including the salience of normal motivational drives (23). By reducing normal salience signals, antipsychotics may actually worsen the negative symptoms of schizophrenia. For example, blockade of DA in the ventral striatum may impair motivation and affective processing (7). Increasing the synaptic specificity of antipsychotics within the striatum could represent one way to improve their efficacy in targeting both the positive and negative symptoms of schizophrenia.

CONCLUSION

Optogenetic studies have allowed for the selective targeting of striatal DA neurons, facilitating functional connectivity analyses, and elucidating much variation in striatal DA signalling at the synaptic level (10). We now know that DA signalling involves co-transmission with glutamate and GABA within distinct striatal regions. Additionally, variations in pre-synaptic receptors, vesicular loading and DA neuron firing contribute to heterogeneity within the striatum. These developments in our understanding of the striatum have helped to provide a neural basis for the motivational-salience theory of psychosis. As our understanding of the complex pathophysiology of schizophrenia continues to advance, we get closer to uncovering novel therapeutic targets. Our current antipsychotic therapies are effective in treating the positive symptoms of schizophrenia yet remain limited in their ability to treat the negative and cognitive symptoms. Therapeutic targets outside of D2 receptor antagonism may be required if the negative and cognitive symptoms of schizophrenia are to be targeted directly. Further research is also required if the underlying disease process of schizophrenia is to be elucidated. Optogenetic studies of dopamine signalling have helped to further our understanding of the complex processes taking place in the striatum at a synaptic level, and may represent one way forward in advancing our understanding of schizophrenia and its treatment.

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