In This Issue

Volume 77, Number 6, March 15, 2015

A brief summary of the articles appearing in this issue of *Biological Psychiatry.*

Mechanisms of Dopamine Regulation and Activation

Rocchetti *et al.* (pages 513–525) investigated the role of dopamine transmission in cognitive deficits in mice. Their data reveals that the dopaminergic projection from the ventral tegmental area to the hippocampus, via dopamine D2 receptor activation, contributes to hippocampal spatial learning and synaptic plasticity. These findings provide a link between dopamine dysregulation and cognitive impairments in psychiatric disorders. They also suggest that antipsychotic medications may impair some forms of learning.

In the brain, the orphan transporter SLC10A4 co-localizes with vesicular monoaminergic transporters, VMAT2 or VAChT, in monoamine neuron terminals. Here, **Larhammar *et al.*** (pages 526–536) assessed the role of SLC10A4 in dopamine-regulated behaviors. They report that, while SLC10A4 does not directly transport dopamine, vesicular uptake of dopamine is increased in the presence of SLC10A4. In addition, mice lacking SLC10A4 showed selective hypersensitivity to psychostimulants, suggesting that SLC10A4 inhibition might be a new strategy to enhance monoamine signaling.

Immune Hypothesis of Schizophrenia

Immune mechanisms may play an important role in psychotic disorders. **Pathmanandavel *et al.*** (pages 537–547) assessed whether antibodies to the dopamine D2 receptor or the *N*-methyl-D-aspartate receptor (NMDAR) were more common in the serum of children having their first episode of psychosis than in healthy children. They detected dopamine D2 receptor or NMDAR antibodies in a subgroup of the children with psychosis but none in controls (18.6% versus 0%). These data suggest that antibodies targeting neural signaling proteins implicated in psychosis may contribute to psychotic states in a subgroup of individuals experiencing psychotic symptoms for the first time.

Immune abnormalities in early life may influence the risk for later development of psychosis. **Nielsen *et al.*** (pages 548–555) analyzed dried blood spots from the Danish Neonatal Screening Biobank to assess inflammatory markers in cases with schizophrenia and controls. Neonatal protein levels were not associated with schizophrenia, suggesting that inflammatory markers at the time of birth do not influence the development of schizophrenia.

NMDA Receptor Effects: Pyramidal Cells and Cortical Connectivity

There is growing evidence for local network disinhibition, i.e., hyperactivity of glutamate neurons in the cortex, in schizophrenia. Deficits in NMDA glutamate receptor signaling may produce disinhibition by directly impairing the activity of GABA interneurons via NMDARs located on these GABA neurons. However, loss of NMDARs on the pyramidal glutamate neurons might also contribute to local network disinhibition. Using a mouse model that eliminated NMDARs selectively on forebrain glutamate neurons by knocking out the GluN1 (NR1) subunit, **Tatard-Leitman *et al.*** (pages 556–568) demonstrate that NMDAR hypofunction in pyramidal cells throughout life is sufficient to cause electrophysiological, molecular, neuropathological, and behavioral changes associated with schizophrenia.

Anticevic *et al.* (pages 569–580) shed new light on the relevance of pharmacologic studies of NMDAR antagonists in animals and humans to the neurobiology of schizophrenia. Using functional magnetic resonance imaging, they characterized and compared patterns of prefrontal cortex functional connectivity at rest in healthy subjects administered the NMDAR antagonist ketamine to the patterns of three groups: 1) individuals at increased genetic risk for developing schizophrenia, 2) patients early in their course of schizophrenia, and 3) patients with chronic schizophrenia. They noted that the overall pattern produced by ketamine, increased frontal cortical functional connectivity, was also evident in the high risk and early course groups. In contrast, patients with chronic illness showed connectivity reductions in lateral prefrontal areas, distinct from ketamine effects. These results suggest that the parallels between the acute effects of ketamine and schizophrenia may be particularly prominent early in the course of schizophrenia.

Hippocampal Subfield Volumes in Psychotic Disorders

The hippocampus consists of anatomically and functionally distinct subfields that may be differentially involved in the pathophysiology of psychotic disorders. In this magnetic resonance imaging study, **Haukvik *et al.*** (pages 581–588) report hippocampal subfield volume reductions in patients with schizophrenia or bipolar disorder, compared to control subjects. The observed volume reductions were greater in patients with schizophrenia, particularly in the presubiculum and subiculum regions, which direct hippocampal outflow to other brain regions.

Prenatal Stress Model Causes Schizophrenia-Like Phenotype

Prenatal stress is considered a risk factor for several neurodevelopmental disorders. Here, **Dong *et al.*** (pages 589–596) provide evidence that DNA methyltransferase 1 and TET-methyldioxygenase 1 are increased in the frontal cortex and hippocampus of mice exposed to prenatal restraint stress. Brain-derived neurotrophic factor (BDNF) transcript levels were decreased, which was accompanied by an enrichment of 5-methylcytosine and 5-hydroxylmethylcytosine levels at corresponding *Bdnf* promoter regions. Patients with psychosis show an epigenetic signature similar to these mice, suggesting that this model may be suitable for studying mechanisms associated with some epigenetic changes in patients with schizophrenia.

ISSN: 0006-3223