

Beyond Dopamine

The lifetime risk for schizophrenia correlated with genetic relatedness
Stages of Development

- Neuronal formation
- Neuronal proliferation
- Proliferation of dendrites and spines
- Synaptogenesis
- Myelination
- Pruning
- Apoptosis

Neuronal Fate in the
Mammalian Cortex

The neurons of the cerebral cortex are generated in the ventricular zone, an epithelial layer of progenitor cells that line the ventricular wall.

Neuronal Fate in the Mammalian Cortex

Once they have left the cell cycle, the immature neurons migrate out of the ventricular zone to form the cortical plate, which eventually becomes the gray matter of the cerebral cortex

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Neuronal Fate in the Mammalian Cortex

The plane of division of progenitor cells in the ventricular zone influences their fate

Neuronal Fate in the Mammalian Cortex

Neuronal Fate in the Mammalian Cortex

Neuronal differentiation does not stop when a cell leaves the cell cycle and migrates to its final position.

Rita Levi-Montalcini observed that death of neurons is a normal occurrence during embryonic development.

Target Cells secrete a variety of neurotrophic factors

Neurotrophin class

- Nerve growth factor
- Brain-derived neurotrophic factor
- Neurotrophin 3
- Neurotrophin 4/5

Interleukin 6 class

- Ciliary neurotrophin factor
- Leukemia inhibitory factor
- Cardiotrophin

Transforming growth factor β class

- Transforming growth factor β 3
- Bone morphogenetic factor
- Glial-derived neurotrophic factor
- Neuroturin
- Persephin
- Artemin

Fibroblast growth factor class

Hepatocyte growth factor

Deprivation of neurotrophic factors activates a cell death program in neurons

The Concept of BRAIN PLASTICITY - Donald Hebb

In 1949, observed that our ability to change our brain through new data and then to learn occurs because of changes at the neuronal cell levels.

The Concept of Long-Term Potentiation

A process by which the size of a neuronal response increases after stimulation. This is probably one of the basis of learning.

The Role of Glutamate

- Glutamate communicates with two receptors: AMPA and NMDA
- LTP is enhanced by glutamate activation of NMDA receptors.

David Hubel and Torsten Wiesel

Both persons explained how experience in the environment affect brain development – a different perspective of brain plasticity.

Two important components of brain plasticity

- Critical periods
- Activity-dependent changes

A Synthetic Model for the Development of Mental Illness

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ORIGINAL DOPAMINE HYPOTHESIS

VERSUS

RECENT AND COMPLEX ROLE OF DOPAMINE

Functional Neuroanatomy of Hallucinations in Schizophrenia
Neuroanatomical Model of Schizophrenia: Prefrontal Inhibition
The Four Major Dopaminergic Tracts in the Brain

Six types of Dopamine Receptors
Dopaminergic Pathways and site of action of various psychoactive substances
Chlorpromazine acting on Dopamine Receptors

Original Dopamine Hypothesis

- DA metabolite and receptor in post-mortem brain do not support this hypothesis (Davis et al, 1991)
 - Some schizophrenic patients do not respond to drugs that block dopamine activity
 - Negative symptoms of schizophrenia are refractory to such drugs
- The Original Dopamine Hypothesis
- Dopamine metabolite and post-mortem brain consistently failed to support the hypothesis
 - A substantiated number of schizophrenic patients are resistant to treatment
 - Drugs that augment dopaminergic activity can not account for the full spectrum of schizophrenia

Metabolite and Receptor Studies

- Drug-free schizophrenic patients tend to exhibit normal or reduced HVA concentration in the CSF
Picker et al., 1990
- The HVA concentration in CSF is inversely related to the magnitude of cortical atrophy
Kahn et al., 1994

SPECT (Single-photon emission computed tomography) as tool

- Cognitive tasks (e.g., Wisconsin Card Sorting Test) among schizophrenic patients fail to show increased frontal lobe blood flow as normal controls.
Weinberger et al., 1986
- Decreased blood flow strongly correlates with low CSF HVA
- Blood Flow increases after administration of dopamine agonists, amphetamine
Davis et al., 1991

DOPAMINERGIC MODEL OF PSYCHOSIS

Psychostimulant psychosis results with increasing doses of amphetamines over prolonged use. Dopaminergic Model of Psychosis

Initial effects are

- Euphoria
- Enhanced attention
- Psychomotor agitation

Dopaminergic Model of Psychosis

On repeated exposure, there are

- Perceptual changes
- Suspiciousness
- Repetitive behavior

Dopaminergic Model of Psychosis

Chronic use leads to:

- Dysphoria
- Paranoid delusions
- Increased distractability
- Ideas of reference
- Auditory, visual, tactile hallucinations

Dopaminergic Model of Psychosis

The key characteristic of psychostimulant psychosis is sensitization, inducing cross-sensitization with other drugs or environmental stressor.

Dopaminergic Model of Psychosis

- Kalivas, in 1995, showed that sensitization is associated with increased stimulant-induced dopamine release in the axon terminals.
- This appears to be a glutamate-dependent process involving both NMDA and non-NMDA receptors.

Dopaminergic Model of Psychosis

Evidences:

- Post-WW II abuse of methamphetamines
- Lieberman et al, in 1987, noted that psychostimulant-naïve schizophrenics become worse when taking psychostimulants.

Dopaminergic Model of Psychosis

- Sensitization is a function of regulatory abnormalities within the cortico-striato-thalamic circuitry.

Is there hyper-dopaminergia in schizophrenia?

Is there Hyperdopaminergia in Schizophrenia

- Studies suggest dysregulation of the mesocortical system maybe closely linked to dysregulation of the mesolimbic and nigrostriatal systems

Complexity of Dopamine

- DA interact with many other neurotransmitter system (Davis, et al, 1991)
- DA is differentially regulated in different brain regions – hypodopaminergic in the cortex; hyperdopaminergic in subcortical areas
- Phenomenon of depolarization blockade A9 and A10.
- Concept of hypofrontality

DOPAMINE HYPOTHESIS

Hypodopaminergic state in cortex may underlie the negative symptoms of schizophrenia

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DOPAMINE HYPOTHESIS

The hyperdopaminergic state in the subcortical area underlie the positive symptoms.

Is there hyperdopaminergic in schizophrenia?

•Grace (1991) presented a model pertinent to dopamine function between the prefrontal cortex and subcortical areas based on 2 events:

- Transient or phasic dopamine release caused by DA firing
- Sustained or tonic release requested by prefrontal cortical areas

Is there hyperdopaminergic in schizophrenia?

New Model Hypothesis:

•Tonic subcortical release of DA would be reduced by decreased activity of cortical efferents leading to an upregulation of subcortical DA receptors, leading to an exaggerated DA response triggered by phasic DA release.

Neuroanatomical Model of Schizophrenia: Prefrontal Inhibition

Serotonergic Model of Psychosis

•In 1954, Gadduan observed LSD-induced psychosis that showed some similarity to 5-HT. This was the first indication of a link between a specific neurotransmitter and psychosis

Serotonergic Model of Psychosis

•LSD demonstrated partial agonist effect on 5-HT_{2A} receptors

The Serotonergic System

- Dorsal raphe nucleus projects to the cortex and striatal areas
- Median raphe nucleus projects to the limbic system

Effects:

- At the midbrain, 5-HT inhibit the firing of dopamine cells projecting from the substantia nigra
- At the striatum and cortex, they inhibit the synaptic release of dopamine

Kapur and Remington, 1996

Serotonergic Model of Psychosis

5-HT_{2A} receptors, which mediate hallucinogenic effects play modulatory roles within local cortical circuits.

Serotonergic Innervation of the Frontal & Piriform Cortex

The Serotonin Hypothesis

- 5-HT projections inhibit DA at two levels:

—At the midbrain, 5-HT inhibits the firing of DA cells from the substantia nigra

—At the cortex and striatum, 5-HT inhibit synaptic release of DA

Glutamate, GABA, and the NMDA Receptor Hypofunction Hypothesis

- Phencyclidine, an NMDA receptor antagonist mimics many positive and negative symptoms of schizophrenia

Javitt and Zukin, 1991

- Tsai et al., 1995 demonstrated reduced levels of glutamate and aspartate in the cortex, as well as reduced activity of the corresponding enzymes

- GABA and glutamate reuptake is reduced in the hippocampus, amygdala and temporal cortex

Convergence of Glutamate, GABA, and Dopamine in the Corticothalamic circuitry

Glutamatergic Model of Psychosis

- Luby in 1959 proposed the “phencyclidine model” of psychosis

GLUTAMATERGIC

MODEL OF PSYCHOSIS

Effects of PCP and ketamine are amply similar to schizophrenia

Glutamatergic Model of Psychosis

- Rosebaum et al, in 1959, Cohen et al, 1962 compared LSD and PCP cognitive effects in healthy subjects compared to schizophrenics.

NMDA Receptor Hypofunction Hypothesis: DA inhibit glutamate release

- NMDA activation causes neuronal degeneration

- NMDA antagonists may ameliorate the symptoms of degeneration

NMDA Receptor Hypofunction Hypothesis:

- NAN and NAP are inhibited by DA antagonists and GABA agonists

Olney and Farber, 1995

NMDA Receptor Hypofunction Hypothesis:

- Olney proposes that NMDA receptors tonically drive GABAergic neurons that inhibit excitatory amino acid neurons.

NMDA Receptor Hypofunction Hypothesis:

- NMDA receptor (NRH) hypofunction would diminish GABAergic inhibition over excitatory inputs to the cortex

NMDA Receptor Hypofunction Hypothesis:

The role of the thalamus

THALAMIC PROJECTIONS -

- Javitt et al., 1994 – treated chronic schizophrenics with glycine – a potentiator of NMDA-receptor mediated neurotransmission.

Glutamatergic Model of Psychosis

GLUTAMATERGIC MODEL OF PSYCHOSIS

Amphetamine-produced paranoia psychosis are associated with relative sparing of cognitive and thought disorder

Glutamatergic Model of Psychosis

- NMDA antagonist psychosis is associated with disorganized thought and behavior, impaired cognitive function and negative symptoms.
- This closely parallels the undifferentiated and disorganized subtypes of schizophrenia.

GLUTAMATERGIC MODEL OF PSYCHOSIS

Paranoid schizophrenia is the most neuroleptic-sensitive

Biochemical Changes associated with Schizophrenia

- Normal or decreased dopamine metabolite in CSF
- Increased striatal D₂ receptors
- Altered expression of D₃ and D₄ mRNA in specific cortical regions
- Decreased cortical glutamate
- Increased cortical glutamate receptors
- Decreased glutamate uptake sites in cingulate cortex
- Decreased GAD mRNA in prefrontal cortex CG
- Increased GABA_A binding sites in cingulate cortex

Evidence of the importance of genetic factors in schizophrenia

Phenomenology of the Model Psychoses

Phenomenology of the Model Psychoses

Indirect effects of anti-schizophrenia drugs on dopamine receptors