Neuroplasticity and Antipsychotics

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One of the most puzzling observations about the mechanism of action of antipsychotic drugs is their delayed therapeutic effect.

This is the rule often in prolonged treatment trials for individual patients until a particular drug has proven to be effective. In some cases, none of the existing drugs will provide remission.

To improve treatment outcome, it seems essential to understand the potential mechanisms that could explain this effect of antipsychotics.
The clinical potency of conventional antipsychotic drugs is directly correlated with their ability to inhibit dopamine D2 receptors, but this relationship cannot explain their delayed action. Since inhibition of D2 receptors should be achieved almost instantaneously, the beneficial therapeutic effect cannot be limited to a straightforward receptor–drug interaction. Moreover, the pharmacological profile of atypical antipsychotics suggests a more complicated mechanism of action.
haloperidol
Which neuronal programs evolve over time?

Neuroplasticity, a gradual process by which the brain adapts to changes in the environment, is a logical consideration in the delayed effects of antipsychotic drugs.
Two processes contribute to neuroplasticity in the adult brain:

1) synaptic plasticity, a remodeling of synapses resulting in the rewiring and strengthening of neural circuits, and

2) neurogenesis, a creation of new neurons.

A demonstration that neuroplasticity conveys some of the therapeutic effects of antipsychotics could provide a valuable target for the design of novel treatment strategies.
Hypothesis

If schizophrenia is a disconnection syndrome caused by inadequate synaptic organization, neuroplasticity induced by antipsychotic drugs can achieve functional and anatomical reconnection.

The time it takes to reestablish proper synaptic function could explain the delayed therapeutic benefits of antipsychotic drugs.
Synaptogenesis during early neuronal development.

(A–C) During early neuronal development, the number of dendritic filopodia decreases while the number of spines increases.

(D) An axonal growth cone and a dendritic filopodium make contact and a molecular adhesion process ensues. (E) Prefabricated protein aggregates get trapped at the presynaptic contact zone and enable the axon to release neurotransmitter.

(F) The release of neurotransmitter triggers the formation of the PSD.
Early synapse formation and developmental processes that could cause schizophrenia

Neurons extend hairlike structures (filopodia) in search for partners to form synapses. A period of extensive synapse formation is followed by synapse stabilization and use-dependent pruning. Synapses that cannot establish communication are removed. This model is supported by developmental studies in the human brain, which show a peak in synapse numbers during the early postnatal period, followed by synapse elimination.

(A) Normal development.

(B), (C) A consistent finding in schizophrenia is a reduction in dendrites and synapses, which is most likely based on a developmental malfunction. Such a reduction can be caused by faulty synapse formation (B), or faulty synapse stabilization (C).
There is agreement that neurogenesis in the mature brain is detectable only in a limited number of brain areas, most notably the hippocampus.
Evidence that haloperidol affects synaptic plasticity

Neuroplasticity can be studied with a variety of methods.

Anatomical techniques quantitatively assess macroscopic features such as regional brain volume, and microscopic features such as the morphology and number of cells, dendrites, dendritic spines, or synapses. Biochemical and molecular techniques assess the state of protein phosphorylation and the regulation of gene expression.

All of these techniques have been applied to elucidate the effect of haloperidol in the striatum, resulting in convincing evidence for volumetric, ultrastructural, and molecular changes.
WHY STRIATUM?

The striatum is the brain area best suited to study neuroplasticity by conventional antipsychotic drugs, although it may not be the principal locus for the cognitive deficits that characterize schizophrenia. Since D2 receptors, the main target for conventional antipsychotic drugs, are abundantly expressed in the striatum, the striatum is the brain area where responses to antipsychotic drug exposure are most noticeable.
Synapse morphology in the striatum

The majority of neurons in the striatum are medium-size with dendritic spines.

Synapses are formed on the dendritic spines as well as on the dendritic shafts (not shown). Synaptic vesicles in the axon terminal release neurotransmitter into the synapse. Neurotransmitters cross the synaptic cleft and interact with receptors in the postsynaptic membrane.

The postsynaptic density (PSD) is an electron dense area that contains receptors, ion channels and scaffolding proteins which anchor receptors to the membrane and facilitate signal transduction.
Haloperidol increases regional brain volume

Neurotrophic effects of haloperidol are supported by morphometric analyses of the caudate and putamen of treated schizophrenic patients. The initial description of striatal enlargement in patients treated with conventional antipsychotics was surprising, but confirmed subsequently. Time-course studies demonstrate that caudate volumes increase during treatment with conventional antipsychotics and normalize after cessation of treatment or when patients are treated with atypical antipsychotics, which have a much weaker impact in the striatum

Haloperidol changes synapse morphology and number

Haloperidol causes ultrastructural changes in synapse morphology in the rat striatum:

• increase in the size of axon terminals
• increase in the absolute number of vesicles
• increase in the size of the postsynaptic density
• increase of glutamatergic synapses
Other brain areas with ultrastructural changes include the substantia nigra and the prefrontal cortex.

*Synaptic plasticity in these affected areas may be involved in reversing the pathophysiology of schizophrenia.*
Molecular modifications during treatment with haloperidol

**Haloperidol affects protein phosphorylation and protein synthesis.**

Protein phosphorylation is involved in signaling processes spanning from synaptic function to gene and protein expression.

Protein phosphorylation and new protein synthesis are required for rapid and long-term synaptic remodeling in the developing and the mature brain.

Learning and memory, the behavioral correlates of neuroplasticity, depend on protein phosphorylation and new protein synthesis.
Haloperidol affects protein phosphorylation

Conventional antipsychotic drugs influence protein phosphorylation via their ability to inhibit D2 receptors.

Inhibition of D2 receptors activates adenylyl cyclase, increases levels of cyclic AMP and activates PKA.

PKA is important for haloperidol-mediated gene induction.

PKA phosphorylates receptors and ion channels at the synapse, and modulates synaptic function and the activity of other protein kinases.
Receptor

Phospholipase C

G-protein

GDP

Adenylate cyclase

GTP

ATP

cAMP

PKA

free Ca++

PiB

IP3

DAG

PKC

calmodulin

dephosphorylation

dephosphorylation

CELLULAR RESPONSES
Haloperidol affects gene expression and new protein synthesis

Gene expression and protein synthesis are essential for various brain functions, notably for the formation of long-term memory.

Haloperidol has been shown to activate levels of many different transcription factor genes in the striatum.

As a consequence, haloperidol affects the regulation of many proteins.
Gene expression and synaptogenesis by haloperidol.

(A) A medium-size spiny neuron in the striatum that expresses D2 receptors contains the transcription factor CREB in the nucleus.

(B) Upon interaction of haloperidol and D2 receptors, PKA is activated and proteins are phosphorylated. Phosphorylation of proteins alters their properties and activities and could be the reason for the perforation of synapses (split PSD). PKA also sets a signal transduction cascade in motion that translocates to the nucleus and phosphorylates the transcription factor CREB. Phosphorylation of CREB at Ser133 enables the expression of genes and proteins that are under the control of Ca2+ and cyclic AMP second messenger pathways.

(C) By incorporating newly synthesized proteins, the dendritic spine splits and yields two synapses. Compensatory mechanisms to slow down synaptogenesis will likely develop. Discontinuation of haloperidol administration reverses the process.
Modulation of receptor function via phosphorylation on the one hand, and via alteration of receptor protein levels on the other, changes the response properties of the affected neurons to presynaptic neurotransmitter release.

The modulation of neuropeptide levels affects the amplitude of postsynaptic stimulation. The alteration in the expression of synaptic proteins is needed for synaptogenesis and the synaptic reorganization observed after chronic haloperidol treatment.
Synaptic plasticity in the mature brain

While synaptogenesis research deals predominantly with the construction of nervous systems during development, haloperidol is usually administered to the mature brain. The current knowledge of synaptic plasticity in the mature brain is therefore of important consideration for our understanding of haloperidol.

Synaptic plasticity is achieved in the mature brain by one of three different mechanisms:
- rearrangement of existing synapses,
- formation of new synapses,
- pruning of existing synapses.
A decrease in synapse number could be caused by an active mechanism such as synapse pruning, or by neuronal death.

While activity strengthens synapses, cells that do not activate postsynaptic neurons have their contacts weakened and eliminated.

This variant of neuroplasticity is important for learning and memory.

The loss of entire neurons in the mature brain, on the other hand, is a pathological rather than plastic phenomenon that is unavoidably accompanied by a loss of synapses.
Ultrastructural analyses show that treatment with haloperidol alters spine shape and density. The observed change in spine shape is indicative of haloperidol’s ability to modulate synaptic strength.

The increase in synapse density observed after treatment with haloperidol is accompanied by an increased synthesis of synaptic proteins.

Synapse splitting seems to be one of the mechanisms responsible for the increase in synapse number. Increase in synapse number, in general, can be observed after enhanced activity in neural circuits or after increased synthesis and release of neurotrophic factors. Haloperidol may employ both mechanisms.
Importantly, the effects of haloperidol are not limited to the striatum!!

Other brain areas implicated in schizophrenia such as the prefrontal cortex, hippocampus and thalamus, are affected as well, albeit to a lesser extent. The action of haloperidol in these brain areas may be more relevant for its antipsychotic properties, but studies from these brain areas are sparse and more ambiguous.
Dopaminergic projections to brain regions implicated in schizophrenia

Most anatomical and molecular studies of antipsychotic drugs have focused on the striatum, since it receives the densest dopaminergic projections and expresses the highest density of dopamine receptors. The effects of antipsychotic drugs on cortex and hippocampus, although more difficult to study, might be more relevant for understanding their antipsychotic effects. Two circuits that are particularly relevant in schizophrenia are highlighted: A reciprocal hippocampus-cortex connection, and the striatal-pallidal-thalamic-cortical loop. Dopaminergic connections are dashed.

Konradi and Heckers, Biol Psychiatry, 2001
What About Atypical Antipsychotic Drugs?

Atypical antipsychotic drugs such as clozapine or olanzapine may have their biggest impact in these brain areas, and they provide valuable information for our understanding of the restorative processes induced by treatment.
What About Atypical Antipsychotic Drugs?

Atypical antipsychotic drugs affect the dopaminergic system to a lesser extent than conventional antipsychotic drugs and, in addition, inhibit serotonergic, muscarinic, histaminergic and $\alpha_1$ adrenergic receptors.
Atypical antipsychotic drugs have a more widespread yet temperate impact across neurotransmitter systems and brain regions.

They are less potent in the striatum, and anatomical changes are generally more subtle and difficult to uncover.

Atypical antipsychotic drugs unquestionably affect neuroplasticity, as they induce gene expression in many brain areas.
In the striatum, atypical antipsychotic drugs induce gene expression to a lesser extent and with a somewhat different distribution than conventional antipsychotic drugs.

Atypical antipsychotics induce genes in brain areas that are implicated in the pathophysiology of schizophrenia, such as the prefrontal cortex.

Atypical antipsychotic drugs hence support the notion that modulation of neuroplasticity in specific brain areas is of critical consideration for the treatment of schizophrenia.
Implications for the treatment and neuropathology of schizophrenia

The delayed therapeutic action of antipsychotic drugs, together with their promotion of neuroplasticity, suggests that the ultrastructural modulation of neuronal circuits is an important contributor to antipsychotic properties.

Despite our focus on the striatum, subtler changes in other brain areas (limbic structures and the prefrontal cortex), may be responsible for, or contribute to, the therapeutic effect of antipsychotic drugs.

Such brain areas show synaptic rearrangements and altered gene expression in response to typical and atypical antipsychotic drug treatment.
Implications for the treatment and neuropathology of schizophrenia

Should antipsychotic drugs indeed ‘rewire’ the brain, such a realization could provide us with new insights into the pathology of schizophrenia.

Recent neuropathology and neuroimaging studies of schizophrenia have provided results that are compatible with the hypothesis that successful treatment of schizophrenia is accomplished by modification of synaptic connectivity.
Taken together, the hypothesis that antipsychotic drug treatment targets synaptic plasticity is consistent with recent evidence of abnormal synaptic function in schizophrenia.

Modulation and facilitation of synaptic plasticity should be considered in future drug development.
Conclusions

There is ample evidence that the typical antipsychotic drug haloperidol affects neuroplasticity in the mature brain. The effect of haloperidol on synapse formation and rearrangement may be important for its antipsychotic properties, and may provide insight into the brain abnormalities leading to schizophrenia.

A further analysis of the role of neuroplasticity in the cause and treatment of schizophrenia could provide us with a novel treatment approach.