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Psychoplastogens: An emerging class of psychotropic drugs

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Abstract
Structural and functional decay of neurons in the prefrontal cortex (PFC) is one of the important factor in the psychopathology of depression and related disorders. The patients taking the currently available antidepressant drugs for treatment these disorders are not much potent in giving immediate beneficial effects. David Olson, Calvin Ly and colleagues investigated the biologic actions of a class of drugs that can more potentially be counteracted by compounds capable of promoting structural and functional neural plasticity in the PFC. They formulated a new class of drugs, the psychoplastogens which includes the compounds like ketamine and some serotonergic psychedelics and entactogens. Through their experiment, they found that these compounds are very potent in inducing neuroplasticity by promoting neuritogenesis and/or spinogenesis and it is achieved by stimulation of a special type of neurotrophic protein called mTOR protein, leaving the exact mechanism behind mTOR stimulation is still unclear.

Keywords: Psychoplastogens, Neuroplasticity, psychotropic drugs, depression

Introduction
The mood disorder depression and anxiety disorders are some of the leading causes of disability among the mentally ill patients worldwide. A condition known as Neural atrophy (Reduction size and change in structure of neurons) in the prefrontal cortex (PFC) occurs mainly due to loss of cytoplasmic proteins causes changes such as the retraction of neurites, loss of dendritic spines and elimination of synapses has an important role in the psychopathology of depression and related disorders, especially loss of dendritic spines is an attribute of depression and other neuropsychiatric disorders. Some of the depression patients do not respond to current antidepressant drugs and those who do will usually require at least some weeks to get initial beneficial effect from the drugs. The 'neuroplasticity', is brain's ability to reorganize itself by forming new neural connections throughout life and which also allows the neurons in the brain to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment.

David Olson, Calvin Ly and colleagues from Department of biochemistry and molecular medicine, UC Davis School of Medicine, California, USA investigated to formulate a new class of drugs from some already available chemical compounds which are more potent and directly promotes the regenerating capacity of the neurons by promoting neuroplasticity. They introduced a new "term 'psychoplastogen' from the Greek roots psych- (mind), -plast (molded), and -gen (producing)."

Meaning
Psychoplastogens are a group of psychoactive compounds capable of rapidly promoting induced neural plasticity and thus causes the nerve cells in the brain to form new neurites and it also enhances the ability of nerve cells to interact with other nerve cells by increasing the number of synapses.

Compounds those are potent as psychoplastogens
A small number of compounds capable of promoting plasticity in the PFC have been identified so far, they are

a) Ketamine: A typical psychoplastogen, most commonly used as an anesthetic agent in animals and sometimes in humans, having some potential risks.

b) Serotonergic psychedelics and entactogens
- Tryptamines: N, N- dimethyltryptamine [DMT] and psilocin
- Amphetamines: 2, 5-dimethoxy 4-iodoamphetamine [DOI] and 3,4 methylene-dioxy-methamphetamine [MDMA]
- Ergolines: Lysergic acid diethylamide [LSD]

c) Others: 7, 8-dihydroxyflavone (DHF)

Indications
- Depression
- post-traumatic stress disorder (PTSD)
- Substance addiction especially heroin addiction

Mechanism of action
By analyzing the effects these compounds in vivo and in vitro by using fluorescence microscopy and electrophysiology, the researchers found that the above compounds especially psychedelics are very potent in promoting neuroplasticity by promoting the following three main processes:

a. **Neuritogenesis:** By forming of new neurites (the first stages of growth, before the axon and dendrites are differentiated) which develop into axons and dendrites.
b. **Spinogenesis:** By the development of dendritic spines in neurons.
c. **Synaptogenesis:** By long developmental process involving synapse formation, synapse maintenance (stabilization) and activity-dependent synapse refinement and elimination, and is important for the establishment of

the neuronal network and the precision of brain circuitry.

The psychedelics are also capable of increasing levels of neurotrophic factors (Proteins regulating various cellular processes including cell proliferation, differentiation, and maturation). The exact mechanisms by which these compounds stimulate mTOR (A protein that helps control several cell functions, including cell division and survival) is not yet clearly understood.

Advantages over the antidepressants used today

- Ketamine is a fast-acting antidepressant when compare to currently available drugs of this category.
- Even very effective among treatment resistant populations
- more effective in treating PTSD and heroin addiction
- Rapid and long-lasting antidepressant and anxiolytic effects even after a single dose including in treatment-resistant populations.

Possible Side Effects

The researchers are hopeful that new medications can be derived from the existing compounds that retain the psychoplastogenic properties while eliminating the side effects. But the ketamine is known to be addictive and has potential risks for its use. The use of both Ketamine and psychedelics currently has a wide variety of mental and physical adverse effects,

The possible physical adverse effects of ketamine:

- Nausea
- Dilated pupils and changes in eyesight
- Inability to control eye movements
- Involuntary muscle movements and muscle stiffness
- Slurred speech
- Numbness
- amnesia
- Slow heart beat
- Increased pressure in the eyes and brain

The possible physical adverse effects of psychedelics.

- An increase in heart rate and blood pressure
- An increase in body temperature
- Loss of appetite
- Nausea and vomiting
- Ataxia and muscular issues

Conclusion

The depression is a disabling mental illness affecting the quality of life of many peoples. There is a need for more potent and safer drugs that will effectively reverse the neuronal decay and thus minimizing the disability. The formulation of a new class of drugs ‘Psychoplastogens ‘is a new hope towards the prevention of disability among patients affected with depression and related disorders.

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