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Review Article

Use of Cognitive Enhancers in Patients with Disorders of Consciousness & Intracranial Injury

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Abstract

This article discusses the use of cognitive enhancers in patients with disorders of consciousness. After intracranial injuries, these agents may support neuroplasticity and overall functional recovery. This article discusses potential mechanisms of such pharmaceutical agents as well as their potential side effects.

Introduction

Cognitive enhancers may support neuroplasticity and overall functional recovery. They have been associated with neuronal sprouting, synaptogenesis and long term potentiation. Methylphenidate and modafinil are effective in restoring arousal in those with damaged reticular activating system (thalamus, brainstem) and bilateral hemispheres. Amantadine is effective in restoring arousal in those with lobar injuries, including after cerebrovascular accident, and post traumatic brain injury including diffuse axonal injury.

Monoaminergic Pathways Implicated in the Use of Cognitive Enhancers

Of the five major monoaminergic pathways of the brain (dopamine, noradrenaline, adrenaline, sertonin, histamine), the catecholamines (dopamine, noradrenaline, adrenaline) are implicated in the mechanisms of cognitive enhancers. Catecholamines are derived from tyrosine (tyrosine --> dopa --> dopamine --> noradrenaline --> adrenaline) [1].

Dopaminergic Pathways

Many dopaminergic cells are located in the midbrain including substantia nigra, pars compacta and ventral tegmentum. This large ascending projection system, mesotelencephalic dopaminergic system, carries input from the basal ganglia, extended amygdala, reticular formation (mesopontine tegmentum) and raphe nuclei. Fibers in this system traverse the internal capsule to the caudate and putamen to form the nigrostriatal dopamine pathway. Other fibers travel through the lateral hypothalamus toward the accumbens and basal forebrain including the basolateral amygdala, septal and olfactory areas. Dopaminergic cells involved in neuroendocrine functions are located in the arcuate and periventricular nuclei of the tuberoinfundibular pathways projecting to the median eminence and posterior pituitary (Figure 1).

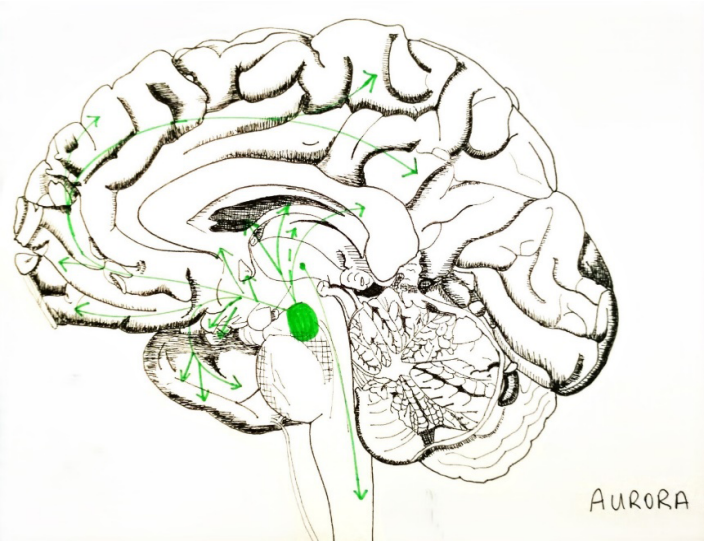

Figure 1: Dopaminergic Pathways.

Noradrenergic and Adrenergic Pathways

Noradrenaline is released from postganglionic sympathetic fibers. Noradrenergic fibers arise from the reticular formation especially pontine locus ceruleus and medullary intermediate reticular zone. Other structures containing high levels of noradrenaline include area postrema (medulla), dorsal nucleus of the vagus, solitary and ambiguus nuclei. Ascending noradrenergic fibers reach brainstem and basal forebrain. Locus ceruleus have widespread projections important in the sleep-wake cycle, wakefulness, attention and vigilance (Figure 2).

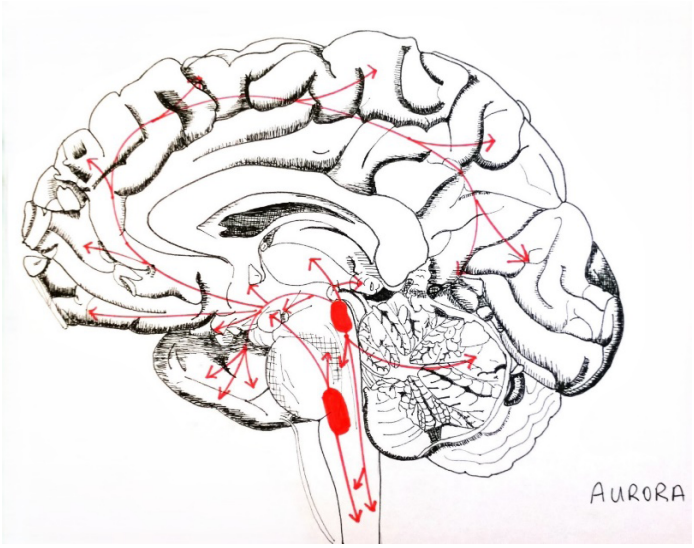

Figure 2: Noradrenergic Pathways.

Methylphenidate

Methylphenidate is a mild CNS stimulant. It inhibits re-uptake of noradrenaline and dopamine into pre-synaptic neurons, increasing monoamine concentrations in the extraneural space. It stimulates both cerebral cortex and subcortical structures, and is associated with increased sympathomimetic activity. Common side effects of methylphenidate may include anxiety, insomnia, GI upset, headache, tachycardia, hypertension and euphoria. Methylphenidate is contraindicated in those with cardiac arrhythmias, cardiac structural abnormalities, severe hypertension, psychosis and hyperthyroidism [2-5].

Amantadine

Amantadine is a weak dopamine agonist with antimuscarinic properties. It is also a weak NDMA receptor antagonist. This medication inhibits presynaptic reuptake of catecholamines and increases dopamine release. Amantadine has been used in the treatment of Parkinson's disease, and also inhibits replication of influenza A virus. Common side effects of amantadine may include anxiety, agitation, orthostasis, hallucinations and breakthrough seizures. This agent is contraindicated in those with gastric ulceration, refractory epilepsy, severe renal impairment and lactation [2-5].

Memantine

Memantine is a derivative of amantadine. It is an NMDA receptor antagonist with potential inhibitory effects on excitotoxic cascades in secondary injury, NMDA-mediated calcium entry into neurons leading to cellular death. Memantine is a neuroprotective agent that also blocks the action of glutamate as a glutamate receptor antagonist. Glutamate may result in excitotoxicity and neuronal cell death, particularly in Alzheimer's disease. This agent has been used to treat moderate to severe Alzheimer's dementia. Common side effects of memantine may include headaches, dizziness, hypertension and impaired balance. This agent is used with caution in those with epilepsy disorder [2,3,4].

Modafinil

Modafinil is a central stimulant with wakefulness promoting effects that selectively inhibits the reuptake of dopamine and noradrenaline. This agent has been associated with stimulation of alpha nonadrenergic receptors, reduced GABA release, increased glutamate or histamine release, as well as altered hypocretin activity. Common side effects of modafinil may include anxiety, headaches and nausea. This agent is contraindicated in those with uncontrolled hypertension, cardiac arrhythmias, mitral valve prolapse, cor pulmonale and pregnancy [2,3,4].

Piracetam

Piracetam is a nootropic cognitive enhancer that acts by improving blood flow, oxygen delivery and glucose utilization in the brain. This medication is a GABAergic agent that restores membrane fluidity and increases cellular levels of energy ATP. It increases acetylcholine levels in the brain. It has neuroprotective and anticonvulsant properties. It improves blood flow by enhancing red blood cell deformability, decreasing platelet aggregability, reducing capillary vasospasm and erythrocyte adhesion to blood vessel walls. Piracetam may be contraindicated in those with cerebral hemorrhage, Huntington's chorea and severe renal impairment [2,3,4,6].

Conclusion

Cognitive enhancers have been safely used as single agents or combination therapies to support early neurorehabilition in those with intracranial injuries. They have been associated with increased arousal and decreased number of ventilator dependent days in the neurocritical care unit. They promote overall enhanced neurological recovery.

Acknowledgement

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