

Huntington's Disease: The Search for Therapeutic Agents

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Huntington disease is an inherited motor disorder of the central nervous system that is progressive and arises from genetically programmed degeneration of brain cells in basal ganglia, cerebral cortex and other regions of the brain [1,2]. The development is related to imbalance of acetylcholine, dopamine, gamma amino butyric acid including other neurotransmitters in the basal ganglia.

Currently, only symptomatic treatments are available for Huntington disease patients. Such treatments involve (i) drug treatments to reduce chorea- involuntary and unwanted movements (examples dopamine antagonists and dopamine depleting agents) (ii) drug treatments for anxiety, depression, irritability and other psychiatric problems (examples neuroleptics, antipsychotics, selective serotonin reuptake inhibitors) (iii) drug treatments and techniques to improve quality and quantity of sleep (example tranquilizers) (iv) miscellaneous drug treatments for other symptoms (examples anticonvulsants, antibiotics) (v) physiotherapy to improve balance, stability and walking (vi) speech and language therapy to assist with speech and swallowing [3,4]. However, research is ongoing to find therapeutic agents (drugs) that will slow down the progression of Huntington disease and possibly cure the neurodegenerative disease. The progress made so far is very promising on the basis of understanding the gene and the abnormal protein (huntingtin - responsible for Huntington's disease) it produces.

The latest and most promising approaches investigated in slowing down the progression of the disease are [5].

Gene "switch off" in animal model of Huntington disease

When gene responsible for the disease was "switched off" in a mouse model after the animal had developed clinical signs, improvement was observed in brain cells and clinical signs. It was therefore postulated that application of the procedure in patients who exhibit symptoms of the disease might lead to clinical improvement in such patients.

Gene silencing therapy

Gene silencing (RNA interference and antisense oligonucleotide therapy) is accomplished in animal model by requesting the cell to ignore a messengerRNA ("switch off" of Huntington disease gene). A messengerRNA is produced when Huntington gene (from DNA) is switched on (transcription) before the protein is built by the cell (translation). This is a very

promising procedure to treat the disease because, unlike in many other diseases, the exact genetic cause of the disease is known. As RNA and DNA molecules do not easily enter the brain, to improve the efficiency of spread of the drugs through the brain, new methods of designing the drug molecules and devices to deliver them directly into the fluid surrounding the brain would be required.

Histone deacetylase inhibitors

Histone deacetylase (HDAC) is an enzyme regulating the “switched on” and “switched off” of genes. It has been found that this process malfunctions in Huntington disease. Histone deacetylase inhibitors have been shown in preclinical trials to be effective in slowing down the cellular damage in the disease. These inhibitors have found application in cancer chemotherapy despite their toxic and serious side effects. Research is ongoing to find more effective histone deacetylase inhibitors with less severe side effects to be tried in humans.

Autophagy activators

Autophagy is a clearance process that cells use to remove unwanted proteins. It was postulated that autophagy enhancers could efficiently assist cells get rid of huntingtin (abnormal protein in Huntington disease) and therefore slow down the disease. Research scientists are of the opinion that drugs that make autophagy happen more efficiently might help cells get rid of huntingtin and live longer since huntingtin (the abnormal protein) responsible for the disease is disposed of using autophagy. Rapamycin was found to slow down the disease in a mouse but not effective in humans when tested in patients with the disease. Research is ongoing to find more efficient, less toxic therapeutic agents that will act as activators of autophagy.

Caspase inhibitors

Caspase inhibitors are agents that antagonize the activities of enzymes called caspases. In cells, huntingtin is cut into smaller proteins by these enzymes. Some of the smaller abnormal protein fragments tend to be more damaging to cells than the abnormal protein itself. Therefore, it was thought the formation of dangerous huntingtin fragments might be prevented by turning off the activities of the enzymes. Minocycline, a therapeutic agent that acts as a caspase inhibitor is undergoing clinical trials as a potential Huntington disease therapeutic agent.

Cystamine and cysteamine therapy

These agents decrease the activity of transglutaminases. The enzymes are believed to be involved in the formation of huntingtin aggregates (lumps of protein) observed in brain cells of Huntington disease patients. In human body, cystamine breaks down into cysteamine. Cystamine has been tried in mice and humans with the disease, however slowing down the disease progression and improvement of movement have only been observed in animals.

Memantine therapy

Memantine, an N-methyl D-aspartate antagonist (NMDA) acts on the glutamatergic system by blocking NMDA glutamate receptors thereby preventing excessive stimulation of brain cells (excitotoxicity) by the chemical transmitter N-methyl D-aspartate. As the drug is utilized to treat moderate to severe form of Alzheimer’s disease (neurodegenerative disease), the drug was therefore thought to be a possible therapy for Huntington’s disease, in terms of relieving the symptoms as well as

slowing down the disease process. Although studies carried out have inconclusive data on memantine as a potential therapeutic agent for the disease further works are ongoing.

p53 pathway inhibition

The accumulation of cell protein (p53) in the brain cells of most Huntington disease patients, led to the hypothesis that there is potential interaction between p53 and huntingtin (abnormal protein). This observation points to the fact that some effects of huntingtin might be due to abnormalities of the p53 pathway or that p53 controls levels of huntingtin. Based on this hypothesis, research is ongoing to minimize the negative effects of huntingtin on cells by identifying targets in the p53 pathway that therapeutic agents might be able to alter its functions.

Kynurenine 3-monooxygenase (KMO) inhibitors

Research has shown that KMO, an enzyme found in microglia, can affect the progresses of Huntington disease. Microglia are the brain's immune system cells and it has been shown that the immune system as well as microglia are overactive in Huntington disease. Therapeutic agents that will switch off KMO, thereby reducing the damage microglia inflict on brain cells were envisaged to be potential KMO inhibitors. Preclinical tests on mice gave promising results.

Dietary supplements therapy

The theory that reduced supply of cellular energy might be a contributing factor in nerve cell death in Huntington disease, has led to the suggestion that dietary supplements such as creatine and coenzyme Q10 have some ability to protect brain cells. Creatine and coenzyme Q10 are dietary supplements known to have the potential to increase the energy efficiency of cells. These supplements may therefore have some ability to protect brain cells. Clinical trials are on them as potential therapeutic agents for Huntington disease.

In conclusion, based on the ongoing research works, we envisage that effective therapeutic agent(s) for Huntington disease will be available in the near future and therefore alleviate the pains and discomfort Huntington patients experience.

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