Nitric Oxide: The Gaseous Culprit of Neurodegeneration

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Neurodegenerative diseases come in many forms, such as Alzheimer's, Parkinson's, and Schizophrenia. Neurodegenerative diseases impact approximately 50 million Americans each year, meaning you probably know someone who has been impacted by it. Unfortunately, out of the many treatments we have today, none are adequate enough to restore a patient's quality of life. However, new pharmacological treatments are being explored by further assessing one gaseous neuromodulator that seems to be implicated in almost every form of neurodegeneration: nitric oxide. In the past decade, researchers have focused on nitric oxide's role in neurodegeneration, including a recent breakthrough paper on the treatment of schizophrenia.

Nitric oxide (NO) is a soluble gas that is found in almost every part of our bodies. There are three isoforms of the synthase (NOS) that produces NO: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Interestingly, every isoform of NOS has been implicated in a variety of neurodegenerative disorders. However, previous research has pointed to nNOS as being the disease-causing agent in the brain (Bredt et. al., 1991). Thus, NO is heavily implicated in neurophysiology and, therefore, the development of many neurodegenerative disorders.

Neurotransmitter release is critical for the proper functioning of the brain. NO has been implicated in regulating neurotransmitter release for dopamine, glutamate, acetylcholine, and more. Previous literature has found nNOS to have comprehensive effects on neurotransmitter release, leading to the development of neurodegeneration, particularly in Schizophrenia and Parkinson's. eNOS, on the other hand, has been found to be neuroprotective by regulating the function and dilation of blood vessels all throughout the brain. iNOS is, by far, the most researched isoform due to the high volume of nitric oxide it produces. It has also been implicated in neurodegeneration previously. However, research has pointed to iNOS's relevance to schizophrenia alone, so some of the previous research involving iNOS has been heavily debated. As of right now, nNOS is the best target for neurodegenerative research, but iNOS is also important for further insight into neurodegeneration and basic brain functioning.

Nitric oxide has been previously implicated in many aspects of cognition, including memory. For researchers interested in improving the memory impairments of schizophrenic patients, the next step was to inhibit nitric oxide production pharmacologically. In a recent paper, researchers explored the effect of using aminoguanidine (AG), an inducible nitric oxide synthase inhibitor.

They began by testing AG along with some other well-known drugs known as ketamine and apomorphine in rats who had schizophrenia. A novel object recognition test (NORT) was performed in order to assess the rats' memory capabilities before and after the drugs ketamine and apomorphine were introduced. This same test was then used to assess the effect of AG. The researchers were able to find a significant difference between the group of rats that received the treatment AG and the group that did not. The rats that received AG as a treatment exhibited more long-term recognition memory, especially when the dose of AG was very high (50 mg/kg). The researchers also found that AG prevented the impairment of long term potentiation, or LTP, which is another form of memory (Lafioniatus, et. al., 2016). However, the current findings are solely behavioral assessments. Unfortunately, on a molecular level, the mechanism underlying these results is still unknown. Researchers must identify the molecular basis of these findings in order to begin drug development and clinical trials in humans.

NO has previously been found to have profound effects on brain functioning and the development of neurodegenerative disorders. The recently published paper discussed above further reiterates the importance of NO. However, further research must be done in order to assess the impact of inhibiting iNOS in the brain. Researchers are not entirely sure of all the functions of the various isoforms of NOS, so it's critical to determine if its inhibition leads to other neurological problems. The recently published schizophrenic research lends some more information pertaining to nitric oxide's role in memory, but there's still more to be discovered. There is a clear relationship developing in the field of neuroscience between NO and neurodegeneration, so further studying NO can be valuable for the treatment of many neurodegenerative disorders. However, before the development of treatment can occur, NO has to be researched much more deeply. The research into NO has only begun, and the future may hold some valuable answers to some of the big questions we have.

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References

Bredt, D., Hwang, P., Glatt, C., Lowenstein, C., Reed, R. and Snyder, S. (1991). Cloned and expressed nitric oxide synthase structurally resembles cytochrome P-450 reductase. Trends in Cell Biology, 1(4), p.86.

Lafioniatis, A., Orfanidou, M., Papadopoulou, E. and Pitsikas, N. (2016). Effects of the inducible nitric oxide synthase inhibitor aminoguanidine in two different rat models of schizophrenia. Behavioural Brain Research, 309, pp.14-21.