Retrospection on the Role of Soluble Guanylate Cyclase in Parkinson’s Disease

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Abstract

Soluble guanylate cyclase (sGC) is an important transducing enzyme of cyclic guanosine monophosphate (cGMP) signaling pathway in striatum which has been considered as a potential target for the treatment of Parkinson’s disease. Etiology of Parkinson’s disease is multifactorial, finally resulting in abnormal proteinopathies causing degeneration of nigrostriatal pathways. Understanding the pathological basis of Parkinson’s disease at molecular level is still an achievable target for the researchers and clinical practitioners. sGCs may be one of the causative factors resulting in Parkinson’s disease due to glutamate toxicity or other event. This review presents the literature from articles of past five decades nearly as still this enzyme protein and its role in Parkinson’s disease is not that clearly understood or presented till date. Recent interventions of this protein inhibition in the treatment of Parkinson’s disease preclinically gave a chance to review the literature about this enzyme and its correlation with factors causing Parkinson’s disease. We explored literature using PubMed and EMBASE for the role of sGC in Parkinson’s disease. Databases were searched using the following terms: Parkinson’s disease, neurotoxins, guanylate cyclase, sGC-cGMP pathway, and neurodegeneration. This review listed out the factors that have probability for stimulating sGC which already have been listed as a neurotoxins causing Parkinson’s disease.

Keywords: Guanylate cyclase inhibitors, guanylyl cyclase, neurodegeneration, neurotoxins, Parkinsonism

Introduction

Parkinsonism is one of the major neurodegenerative disorders worldwide. Substantia nigra pars compacta of the central nervous system exhibits differential vulnerability to various etiological factors of Parkinson’s disease. Parkinson’s disease results from several pathological and molecular events that provoke neurodegeneration of dopaminergic neurons. Soluble guanylate cyclase (sGC) enzyme was reported abundantly in striatal medium spiny neurons (MSN). MSNs were largely located in direct and indirect tracts of the basal ganglia and involved in normal physiological functions of the basal ganglia such as motor activity control as demonstrated in Figure 1. The direct pathways include D1 receptors which increase excitatory thalamic input to cerebral cortex and increase the motor activity. The indirect tracts include D2 receptors which decrease the thalamic input to cerebral cortex and the motor activity. In Parkinson’s disease, MSN degeneration is due to various pathological and molecular mechanisms. These molecular and pathological changes in Parkinson’s disease may lead to movement disorders such as hypokinesia, tremors, molecular rigidity, slowing of gait, and reduced agility. This neuronal dysfunction may be aggravated due to persistent activation of neuronal pathways, leading to Parkinson’s disease. Cyclic guanosine monophosphate (cGMP) pathway was considered to be potential pathway in neurotransmission at striatal level. sGC is an important enzyme protein in cGMP pathway which when derailed may be a causative factor for Parkinson’s disease or aggravation of changes in Parkinson’s disease. As pathogenesis of Parkinson’s disease is multifactorial, sGC-cGMP pathway was considered to review the role of sGC as a causative factor. The effect of neurotoxins on sGC in Parkinson’s disease may be considered as a potential target for the treatment of Parkinson’s disease.

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Parkinson’s disease and sGC inhibitors in Parkinson’s disease was reviewed. The role of sGC in neurodegeneration and Parkinson’s disease was reviewed by exploring the literature using PubMed and EMBASE. Databases were searched using the following terms: Parkinson’s disease, neurotoxins, guanylate cyclase, sGC-cGMP pathway, and neurodegeneration.

**Soluble Guanylate Cyclases**

sGC (EC 4.6.1.2) is a type of guanylate cyclase enzyme belonging to the family lyases. Structurally sGC is a heterodimeric family consisting of two subunits α and β [Figure 2]. α1, α2, α2i, β1, β2 are the isoforms of sGC. Most common sGC isoform in the brain is α1β1, and α2 was also found in the human fetal brain. β subunit consists of enzyme activating site with heme residues, but both subunits are required for activating the enzyme. This enzyme can be affected by neurotransmitters in the brain increasing cGMP levels which is responsible for glutamate neurotransmission and chronic effects in synaptic transmission. Localization of sGC in the specific regions of the brain may be related to some of the abnormalities in a pathological state or to the pathological condition of a particular part of the brain. An in situ hybridization study of rat brain revealed that sGC activity in striatum is 2.5–3 times more in comparison to other parts of the brain [Figure 3]. Immunohistochemical findings of a study had revealed the presence of guanylate cyclase activity abundant in caudate putamen complex but could not state whether it is a soluble type or particulate type of guanylate cyclase.

**Soluble Guanylate Cyclase-cyclic Guanosine Monophosphate Pathway in Parkinsonism**

sGC-cGMP pathway is a physiological process for synthesis of cGMP from guanosine triphosphate which leads to the activation of protein kinases to cause various biochemical changes at cellular level. Stimulation of sGC increases cellular Ca²⁺ levels due to activation of protein kinase-dependent ion channels. This increased Ca²⁺ causes stimulation of glutamate receptors responsible for glutamate transmission in MSN of direct and indirect dopaminergic tracts. This glutamate in turn also regulates the sGC activation through regulation of neuronal nitric oxide (NO) synthase or through phosphodiesterases, which metabolizes cGMP. When there is excess stimulation of sGC, it causes glutamate toxicity and apoptosis. These are the normal and abnormal events of the sGC-cGMP pathway [Figure 4].

Pathological consequences of this pathway may be excess glutamate transmission, resulting in abnormal motor behavior in the animals or humans, and this glutamate toxicity may cause generation of reactive oxygen species (ROS) at cellular level, leading to apoptosis of neuronal cells in dopaminergic tracts. Over-expression of this enzyme may be of various reasons which may also include genetic variations or abnormalities. First factor of over-expression of sGC may be excess stimulation causing excess production of cGMP which in turn leads to excess glutamate activity. This augmented glutamate activity was considered toxic leading to apoptosis of neurons which may be caspase dependent or independent depending on the site of excess glutamate activity in the brain. The excess glutamate activity causes influx of Ca²⁺ ions into neurons which leads to increase Ca²⁺ ion concentration intracellularly. This results in mitochondrial dysfunction leading to inhibition of respiratory chain and ROS accumulation. These mitochondrial dysfunction and ROS generation signals may activate caspase-dependent apoptosis. Here, activation of sGC was reviewed and listed various factors which may activate sGC and be a causative factor for Parkinson’s disease or an aggravation factor for the disease symptoms of Parkinson’s disease. Apart from NO which has been considered as the principal activator of sGC, carbon monoxide (CO), lead (Pb²⁺), manganese (Mn²⁺), aluminum (Al³⁺),...
Aluminum exposure is common as its availability is 8% (approximately) in the earth crust. It is being exposed to humans in various forms through air, food, and water. There are clinical studies which had reported the involvement of aluminum in Parkinson’s disease. Alumimum in the form of salts such as aluminum citrate and aluminum sulfate was reported to increase cyclic GMP levels variably at different sites of brain; this may involve the role of sGC. Further, studies are required to evaluate role of sGC stimulated by aluminum leading to Parkinson’s disease.

MPTP is a neurotoxin, increasing the activity of sGC and raising the levels of cGMP in the brain, particularly in striatal neurons. This may lead to increased glutamate activity and result in apoptosis of striatal neurons. Another neurotoxin 6-OHDA has also been reported to increase the striatal cGMP levels abnormally, which may indicate its role in activation of sGC and striatal neurons apoptosis.

Paraquat, as a pesticide neurotoxin causing Parkinson’s disease both in human and animals is known. Preclinical studies reported that paraquat had caused loss of striatal fibers in a dose-dependent manner. There are studies which revealed increase in NO activity when subjected to paraquat and also competitive inhibition of paraquat-induced ROS formation by methylene blue which is an sGC inhibitor. The direct activity of paraquat with sGC in the brain is not yet known, but it is known to stimulate particulate guanylate cyclase and increase the levels of cGMP in the lungs resulting cystic fibrosis.

**Role of Soluble Guanylate Cyclase Inhibitors in Parkinsonism**

In the above section, the importance of sGC in etiopathogenesis of Parkinson’s disease has been demonstrated. Now, it may be stated that use of guanylate cyclase inhibitors may stop the progression of Parkinson’s disease which may attenuate the apoptosis of striatal neurons. Preclinical studies reported that sGC inhibitor such as 1H-[1,2,4] oxadiazolo-[4,3-a] quinoxalin-1-one improved corticostriatal synaptic transmission and the motor behavior in mice models of MPTP and 6-OHDA. Another study reported the presence of endogenous sGC inhibitor (CCTn) which inhibits the enzyme in a different manner without affecting the binding of NO. Zn2+, Cd2+, and Hg2+ have shown inhibitory effect on guanylate cyclase. Further studies can be made in more detail
to achieve the long-term safety of these drugs preclinically for their clinical usage.

**Conclusion**

sGC being the key enzyme for the synthesis of cGMP and one of the responsible factors for causing apoptosis through glutamate toxicity may be considered as a causative factor or aggravating factor of Parkinson’s disease. This review listed out the factors that have probability for stimulating sGC which was already listed as neurotoxins causing Parkinson’s disease. As Parkinson’s disease is multifactorial and is likely to involve different causes in different patients, there is a necessity to identify an alternative nondopaminergic mechanism. The sGC-cGMP signaling cascade is an emerging candidate for second messenger-based therapies of Parkinson’s disease. Genetic variability and polymorphism of sGC in the brain can also be studied to improve the treatment strategies of Parkinson’s disease.

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**Conflicts of interest**

There are no conflicts of interest.

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