

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

Mohankrishna Ghanta, Elango Panchanathan, Bhaskar V. K. S. Lakkakula<sup>1</sup>, Anbumani Narayanaswamy<sup>2</sup>

Departments of Pharmacology and <sup>2</sup>Microbiology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra University, Porur, Chennai, Tamil Nadu,

<sup>1</sup>Department of Molecular Genetics, Research Division, Sickle Cell Institute Chhattisgarh, Raipur, Chhattisgarh, India

## 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.<sup>[1,2]</sup> 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<sup>[3-5]</sup> and involved in normal physiological functions of the basal ganglia such as motor activity control<sup>[6]</sup> as demonstrated in Figure 1. The direct pathways include D<sub>1</sub> receptors which increase excitatory thalamic input to cerebral cortex and increase the motor activity. The indirect tracts include D<sub>2</sub> 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.<sup>[7]</sup> This neuronal dysfunction may be aggravated due to persistent activation of neuronal pathways, leading to Parkinson's disease.<sup>[8]</sup> Cyclic guanosine monophosphate (cGMP) pathway was considered to be potential pathway in neurotransmission at striatal level.<sup>[9]</sup> sGC is an important enzyme protein in cGMP pathway<sup>[10]</sup> 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

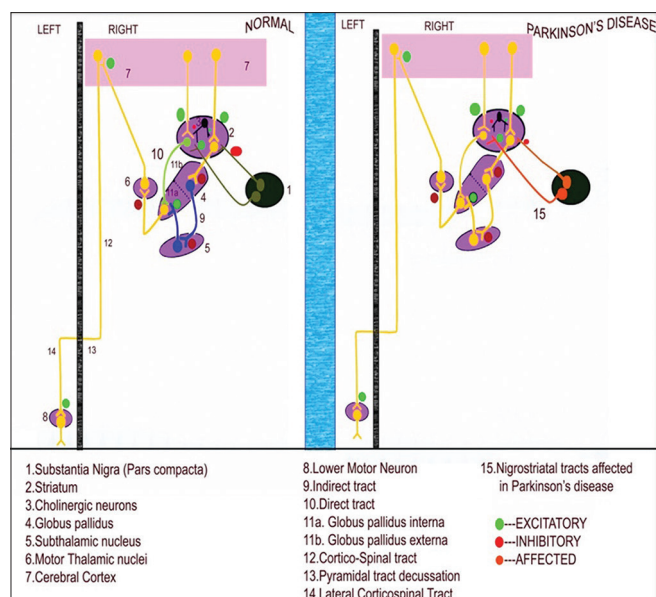
**Address for correspondence:** Elango Panchanathan,  
Department of Pharmacology, Sri Ramachandra Medical College and  
Research Institute, Sri Ramachandra University, Porur,  
Chennai - 600 116, Tamil Nadu, India.  
E-mail: drpelango@yahoo.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** [reprints@medknow.com](mailto:reprints@medknow.com)

**How to cite this article:** Ghanta M, Panchanathan E, Lakkakula BV, Narayanaswamy A. Retrospection on the role of soluble guanylate cyclase in parkinson's disease. J Pharmacol Pharmacother 2017;8:87-91.

**Received:** 24-03-2017 **Revised:** 06-07-2017 **Accepted:** 09-08-2017



**Figure 1:** Basal ganglia pathways in Parkinson's disease

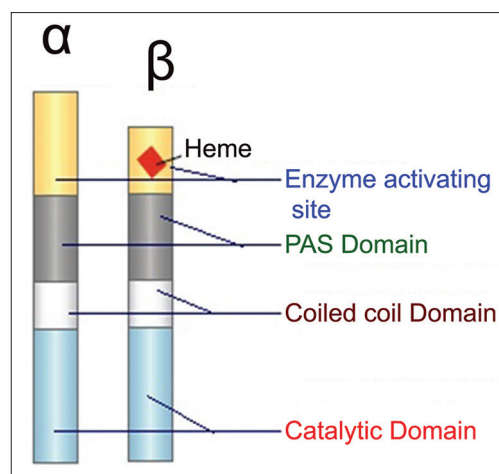
Parkinson's disease and sGC inhibitors in Parkinson's disease was reviewed. The role of sGC in neurodegeneration and Parkinson's disease was reviewed by exploring the literature using PubMed and EMBASE. Databases were searched using the following terms: Parkinson's disease, neurotoxins, guanylate cyclase, 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.<sup>[11]</sup> Structurally sGC is a heterodimeric protein compound consisting of two subunits  $\alpha$  and  $\beta$  [Figure 2].  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 2i$ ,  $\beta 1$ ,  $\beta 2$  are the isoforms of sGC.<sup>[12,13]</sup> Most common sGC isoform in the brain is  $\alpha 1\beta 1$ ,<sup>[14,15]</sup> and  $\alpha 2$  was also found in the human fetal brain.<sup>[16]</sup>  $\beta$  subunit consists of enzyme activating site with heme residues, but both subunits are required for activating the enzyme.<sup>[17]</sup> This enzyme can be affected by neurotransmitters in the brain<sup>[18]</sup> increasing cGMP levels<sup>[19]</sup> which is responsible for glutamate neurotransmission and chronic effects in synaptic transmission.<sup>[20]</sup> 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<sup>[21]</sup> [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.<sup>[22]</sup>

## SOLUBLE GUANYLATE CYCLASE- CYCLIC GUANOSINE MONOPHOSPHATE PATHWAY IN PARKINSONISM

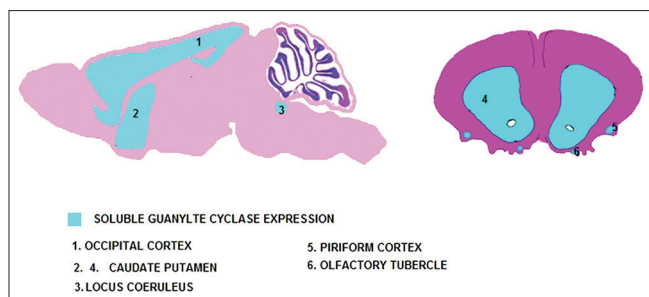
sGC-cGMP pathway is a physiological process for synthesis of cGMP from guanosine triphosphate which leads to the



**Figure 2:** Structure of soluble guanylate cyclase

activation of protein kinases to cause various biochemical changes at cellular level.<sup>[23]</sup> Stimulation of sGC increases cellular  $\text{Ca}^{+2}$  levels due to activation of protein kinase-dependent ion channels.<sup>[24]</sup> This increased  $\text{Ca}^{+2}$  causes stimulation of glutamate receptors responsible for glutamate transmission in MSN of direct and indirect dopaminergic tracts.<sup>[25,26]</sup> This glutamate in turn also regulates the sGC activation through regulation of neuronal nitric oxide (NO) synthase<sup>[27]</sup> or through phosphodiesterases, which metabolizes cGMP.<sup>[28,29]</sup> 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,<sup>[30,31]</sup> and this glutamate toxicity may cause generation of reactive oxygen species (ROS) at cellular level, leading to apoptosis of neuronal cells in dopaminergic tracts.<sup>[32,33]</sup> 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.<sup>[34]</sup> This augmented glutamate activity was considered toxic leading to apoptosis of neurons<sup>[35]</sup> which may be caspase dependent or independent depending on the site of excess glutamate activity in the brain.<sup>[36,37]</sup> The excess glutamate activity causes influx of  $\text{Ca}^{+2}$  ions into neurons which leads to increase  $\text{Ca}^{+2}$  ion concentration intracellularly.<sup>[38]</sup> 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.<sup>[37,39]</sup> 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,<sup>[40]</sup> carbon monoxide (CO), lead ( $\text{Pb}^{+2}$ ), manganese ( $\text{Mn}^{+2}$ ), aluminum ( $\text{Al}^{+3}$ ),



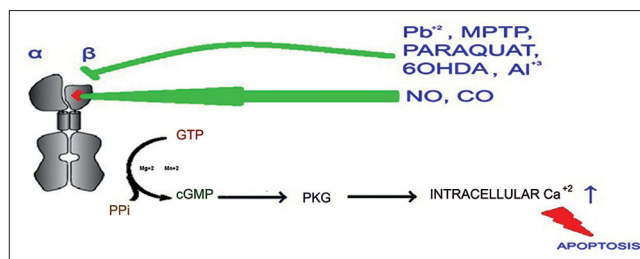
**Figure 3:** Guanylate cyclase location in the rat brain

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), hydroxydopamine (6-OHDA), and paraquat may also affect the sGC activity.

CO is abundantly available in the environment due to pollution.<sup>[41]</sup> This can chronically affect the sGC leading to the changes in striatum.<sup>[42]</sup> CO exposure resulting in Parkinson's disease was reported by many observational studies all over the world.<sup>[43-46]</sup> CO binds to heme part of sGC at the same binding site of NO<sup>[47]</sup> and causes its stimulation by formation of carbonyl-heme complex.<sup>[48,49]</sup> Preclinical studies revealed that CO can stimulate sGC but not as strong as NO.<sup>[48]</sup> Although CO is a weak stimulator of sGC, it may not have controlling mechanisms such as NO. Stimulation of sGC with NO is regulated by glutamate-dependent neuronal NO synthase. Hence, there may be a considerable effect due to CO on sGC affecting striatal dopaminergic system through glutamate toxicity. A study reported that CO may also be formed from hemeoxygenase in the brain.<sup>[50]</sup> There may be aggravation of CO action on sGC either by increased CO levels in corpus striatum or due to compromise in neurotrophic factors and glutathione.

Pb<sup>2+</sup> exposure although controlled in many ways by regulation of pollution boards and food and drug regulatory bodies, there is still considerable exposure to humans through various sources<sup>[51,52]</sup> affecting or causing diseases even at blood lead levels of <10µg/dL.<sup>[53,54]</sup> Clinical studies have reported increased risk of Parkinson's disease upon exposure to lead substances.<sup>[55]</sup> Till now, direct effects of Pb on sGC in the brain were not reported, but it may affect indirectly by causing accumulation of arachidonic acid<sup>[56]</sup> which is also a stimulator of sGC similar to CO and NO.<sup>[57]</sup> Some studies revealed that there is downregulation of sGC activity in the aorta when subjected to lead in an hypertension animal model.<sup>[58]</sup> Further studies are required to evaluate the effects of lead on sGC in brain.

Magnesium (Mg<sup>2+</sup>) is an important factor facilitating production of cGMP as a cofactor for the enzyme reaction.<sup>[59,60]</sup> Activity of guanylate cyclase is more active with Mn<sup>2+</sup> than Mg<sup>2+</sup>,<sup>[61]</sup> but selectivity of Mn<sup>2+</sup> on the type of guanylate cyclase has to be studied. Here, it may be concluded that any association or availability of even weak stimulators of sGC with increased Mg<sup>2+</sup> or Mn<sup>2+</sup> levels in the brain may lead to excess cGMP formation and glutamate toxicity in brain.



**Figure 4:** Soluble guanylate cyclase-cyclic guanosine monophosphate pathway

Aluminum exposure is common as it's 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.<sup>[62-65]</sup> Aluminum 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;<sup>[66]</sup> 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.<sup>[67]</sup> 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,<sup>[68]</sup> 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<sup>[69]</sup> and animals,<sup>[70]</sup> is known. Preclinical studies reported that paraquat had caused loss of striatal fibers in a dose-dependent manner.<sup>[71-74]</sup> There are studies which revealed increase in NO activity when subjected to paraquat<sup>[75]</sup> and also competitive inhibition of paraquat-induced ROS formation by methylene blue which is an sGC inhibitor.<sup>[76]</sup> 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.<sup>[77]</sup>

## 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.<sup>[68]</sup> Another study reported the presence of endogenous sGC inhibitor (CCTη) which inhibits the enzyme in a different manner without affecting the binding of NO.<sup>[78]</sup> Zn<sup>2+</sup>, Cd<sup>2+</sup>, and Hg<sup>2+</sup> have shown inhibitory effect on guanylate cyclase.<sup>[61]</sup> 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.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Mattson MP, Magnus T. Ageing and neuronal vulnerability. *Nat Rev Neurosci* 2006;7:278-94.
- Saxena S, Caroni P. Selective neuronal vulnerability in neurodegenerative diseases: From stressor thresholds to degeneration. *Neuron* 2011;71:35-48.
- Le Moine C, Bloch B. D1 and D2 dopamine receptor gene expression in the rat striatum: Sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. *J Comp Neurol* 1995;355:418-26.
- Bateup HS, Svenningsson P, Kuroiwa M, Gong S, Nishi A, Heintz N, *et al.* Cell type-specific regulation of DARPP-32 phosphorylation by psychostimulant and antipsychotic drugs. *Nat Neurosci* 2008;11:932-9.
- Bertran-Gonzalez J, Bosch C, Maroteaux M, Matamalas M, Hervé D, Valjent E, *et al.* Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. *J Neurosci* 2008;28:5671-85.
- Lanciego JL, Luquin N, Obeso JA. Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med* 2012;2:a009621.
- Baron MS. Movement disorders in the older patient: Differential diagnosis and general management. *Cleve Clin J Med* 2005;72 Suppl 3:S38-51.
- Jové M, Portero-Otín M, Naudi A, Ferrer I, Pamplona R. Metabolomics of human brain aging and age-related neurodegenerative diseases. *J Neuropathol Exp Neurol* 2014;73:640-57.
- Polito M, Klarenbeek J, Jalink K, Paupardin-Tritsch D, Vincent P, Castro LR, *et al.* The NO/cGMP pathway inhibits transient cAMP signals through the activation of PDE2 in striatal neurons. *Front Cell Neurosci* 2013;7:211.
- Garthwaite J. Concepts of neural nitric oxide-mediated transmission. *Eur J Neurosci* 2008;27:2783-802.
- Denninger JW, Marletta MA. Guanylate cyclase and the .NO/cGMP signaling pathway. *Biochim Biophys Acta* 1999;1411:334-50.
- Derbyshire ER, Marletta MA. Structure and regulation of soluble guanylate cyclase. *Annu Rev Biochem* 2012;81:533-59.
- Kamisaki Y, Saheki S, Nakane M, Palmieri JA, Kuno T, Chang BY, *et al.* Soluble guanylate cyclase from rat lung exists as a heterodimer. *J Biol Chem* 1986;261:7236-41.
- Ibarra C, Nedvetsky PI, Gerlach M, Riederer P, Schmidt HH. Regional and age-dependent expression of the nitric oxide receptor, soluble guanylyl cyclase, in the human brain. *Brain Res* 2001;907:54-60.
- Burette A, Zabel U, Weinberg RJ, Schmidt HH, Valtchanoff JG. Synaptic localization of nitric oxide synthase and soluble guanylyl cyclase in the hippocampus. *J Neurosci* 2002;22:8961-70.
- Harteneck C, Wedel B, Koesling D, Malkewitz J, Böhme E, Schultz G, *et al.* Molecular cloning and expression of a new alpha-subunit of soluble guanylyl cyclase. Interchangeability of the alpha-subunits of the enzyme. *FEBS Lett* 1991;292:217-22.
- Buechler WA, Nakane M, Murad F. Expression of soluble guanylate cyclase activity requires both enzyme subunits. *Biochem Biophys Res Commun* 1991;174:351-7.
- Kebabian JW. Biochemical regulation and physiological significance of cyclic nucleotides in the nervous system. *Adv Cyclic Nucleotide Res* 1977;8:421-508.
- Schulz S, Yuen PS, Garbers DL. The expanding family of guanylyl cyclases. *Trends Pharmacol Sci* 1991;12:116-20.
- Shibuki K, Okada D. Endogenous nitric oxide release required for long-term synaptic depression in the cerebellum. *Nature* 1991;349:326-8.
- Matsuoka I, Giuli G, Poyard M, Stengel D, Parma J, Guellaen G, *et al.* Localization of adenylyl and guanylyl cyclase in rat brain by *in situ* hybridization: Comparison with calmodulin mRNA distribution. *J Neurosci* 1992;12:3350-60.
- Ariano MA, Lewicki JA, Brandwein HJ, Murad F. Immunohistochemical localization of guanylate cyclase within neurons of rat brain. *Proc Natl Acad Sci U S A* 1982;79:1316-20.
- Lucas KA, Pitari GM, Kazerounian S, Ruiz-Stewart I, Park J, Schulz S, *et al.* Guanylyl cyclases and signaling by cyclic GMP. *Pharmacol Rev* 2000;52:375-414.
- Murad F. Shattuck lecture. Nitric oxide and cyclic GMP in cell signaling and drug development. *N Engl J Med* 2006;355:2003-11.
- Tsou K, Snyder GL, Greengard P. Nitric oxide/cGMP pathway stimulates phosphorylation of DARPP-32, a dopamine- and cAMP-regulated phosphoprotein, in the substantia nigra. *Proc Natl Acad Sci U S A* 1993;90:3462-5.
- Nishi A, Watanabe Y, Higashi H, Tanaka M, Nairn AC, Greengard P, *et al.* Glutamate regulation of DARPP-32 phosphorylation in neostriatal neurons involves activation of multiple signaling cascades. *Proc Natl Acad Sci U S A* 2005;102:1199-204.
- Dinerman JL, Steiner JP, Dawson TM, Dawson V, Snyder SH. Cyclic nucleotide dependent phosphorylation of neuronal nitric oxide synthase inhibits catalytic activity. *Neuropharmacology* 1994;33:1245-51.
- Hepp R, Tricoire L, Hu E, Gervasi N, Paupardin-Tritsch D, Lambollez B, *et al.* Phosphodiesterase type 2 and the homeostasis of cyclic GMP in living thalamic neurons. *J Neurochem* 2007;102:1875-86.
- Lin DT, Fretier P, Jiang C, Vincent SR. Nitric oxide signaling via cGMP-stimulated phosphodiesterase in striatal neurons. *Synapse* 2010;64:460-6.
- Jouvert P, Revel MO, Lazaris A, Aunis D, Langley K, Zwiller J, *et al.* Activation of the cGMP pathway in dopaminergic structures reduces cocaine-induced EGR-1 expression and locomotor activity. *J Neurosci* 2004;24:10716-25.
- Schmidt CJ, Chapin DS, Cianfrogna J, Corman ML, Hajos M, Harms JF, *et al.* Preclinical characterization of selective phosphodiesterase 10A inhibitors: A new therapeutic approach to the treatment of schizophrenia. *J Pharmacol Exp Ther* 2008;325:681-90.
- Froissard P, Duval D. Cytotoxic effects of glutamic acid on PC12 cells. *Neurochem Int* 1994;24:485-93.
- Behl C, Widmann M, Trapp T, Holsboer F. 17-beta estradiol protects neurons from oxidative stress-induced cell death *in vitro*. *Biochem Biophys Res Commun* 1995;216:473-82.
- Garthwaite J, Charles SL, Chess-Williams R. Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. *Nature* 1988;336:385-8.
- Li Y, Maher P, Schubert D. Requirement for cGMP in nerve cell death caused by glutathione depletion. *J Cell Biol* 1997;139:1317-24.
- Zhang Y, Lu X, Bhavnani BR. Equine estrogens differentially inhibit DNA fragmentation induced by glutamate in neuronal cells by modulation of regulatory proteins involved in programmed cell death. *BMC Neurosci* 2003;4:32.

37. Zhang Y, Bhavnani BR. Glutamate-induced apoptosis in primary cortical neurons is inhibited by equine estrogens via down-regulation of caspase-3 and prevention of mitochondrial cytochrome c release. *BMC Neurosci* 2005;6:13.
38. Duchen MR. Mitochondria and calcium: From cell signalling to cell death. *J Physiol* 2000;529(Pt 1):57-68.
39. Atlante A, Calissano P, Bobba A, Giannattasio S, Marra E, Passarella S, *et al.* Glutamate neurotoxicity, oxidative stress and mitochondria. *FEBS Lett* 2001;497:1-5.
40. Ignarro LJ. Signal transduction mechanisms involving nitric oxide. *Biochem Pharmacol* 1991;41:485-90.
41. Jaffe LS. Ambient carbon monoxide and its fate in the atmosphere. *J Air Pollut Control Assoc* 1968;18:534-40.
42. Ringel SP, Klawans HL Jr. Carbon monoxide-induced Parkinsonism. *J Neurol Sci* 1972;16:245-51.
43. Sohn YH, Jeong Y, Kim HS, Im JH, Kim JS. The brain lesion responsible for parkinsonism after carbon monoxide poisoning. *Arch Neurol* 2000;57:1214-8.
44. Choi IS. Parkinsonism after carbon monoxide poisoning. *Eur Neurol* 2002;48:30-3.
45. Marcinko Budincevic A, Pavlovic T, Soldo Koruga A, Budincevic H. Parkinsonism due to fahr's disease with previous carbon monoxide intoxication. *Acta Neurol Belg* 2015;115:689-90.
46. Kao HW, Cho NY, Hsueh CJ, Chou MC, Chung HW, Liou M, *et al.* Delayed parkinsonism after CO intoxication: Evaluation of the substantia nigra with inversion-recovery MR imaging. *Radiology* 2012;265:215-21.
47. Vogel KM, Hu S, Spiro TG, Dierks EA, Yu AE, Burstyn JN, *et al.* Variable forms of soluble guanylyl cyclase: Protein-ligand interactions and the issue of activation by carbon monoxide. *J Biol Inorg Chem* 1999;4:804-13.
48. Stone JR, Marletta MA. Soluble guanylate cyclase from bovine lung: Activation with nitric oxide and carbon monoxide and spectral characterization of the ferrous and ferric states. *Biochemistry* 1994;33:5636-40.
49. Kharitonov VG, Sharma VS, Pilz RB, Magde D, Koesling D. Basis of guanylate cyclase activation by carbon monoxide. *Proc Natl Acad Sci U S A* 1995;92:2568-71.
50. Verma A, Hirsch DJ, Glatt CE, Ronnett GV, Snyder SH. Carbon monoxide: A putative neural messenger. *Science* 1993;259:381-4.
51. Moawad EM, Badawy NM, Manawill M. Environmental and occupational lead exposure among children in Cairo, Egypt: A community-based cross-sectional study. *Medicine (Baltimore)* 2016;95:e2976.
52. Fewtrell LJ, Prüss-Ustün A, Landrigan P, Ayuso-Mateos JL. Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure. *Environ Res* 2004;94:120-33.
53. Canfield RL, Henderson CR Jr., Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP, *et al.* Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. *N Engl J Med* 2003;348:1517-26.
54. Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. *Neurotoxicol Teratol* 2004;26:359-71.
55. Weisskopf MG, Weuve J, Nie H, Saint-Hilaire MH, Sudarsky L, Simon DK, *et al.* Association of cumulative lead exposure with Parkinson's disease. *Environ Health Perspect* 2010;118:1609-13.
56. Dorman RV, Freeman EJ. Lead-dependent effects on arachidonic acid accumulation and the proliferation of vascular smooth muscle. *J Biochem Mol Toxicol* 2002;16:245-53.
57. Hawkins RD, Son H, Arancio O. Nitric oxide as a retrograde messenger during long-term potentiation in hippocampus. *Prog Brain Res* 1998;118:155-72.
58. Farmand F, Ehdaie A, Roberts CK, Sindhu RK. Lead-induced dysregulation of superoxide dismutases, catalase, glutathione peroxidase, and guanylate cyclase. *Environ Res* 2005;98:33-9.
59. Russwurm M, Koesling D. NO activation of guanylyl cyclase. *EMBO J* 2004;23:4443-50.
60. Cary SP, Winger JA, Marletta MA. Tonic and acute nitric oxide signaling through soluble guanylate cyclase is mediated by nonheme nitric oxide, ATP, and GTP. *Proc Natl Acad Sci U S A* 2005;102:13064-9.
61. Hardman JG, Sutherland EW. Guanyl cyclase, an enzyme catalyzing the formation of guanosine 3',5'-monophosphate from guanosine triphosphate. *J Biol Chem* 1969;244:6363-70.
62. Yasui M, Kihira T, Ota K. Calcium, magnesium and aluminum concentrations in Parkinson's disease. *Neurotoxicology* 1992;13:593-600.
63. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, *et al.* Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of parkinson's disease. *Neurotoxicology* 1999;20:239-47.
64. Burkhart CG, Burkhart CN. Aluminum alters sweating by constricting the dermal duct lumen. *Int J Dermatol* 2008;47:1306-7.
65. Altmann P, Cunningham J, Dhanesha U, Ballard M, Thompson J, Marsh F, *et al.* Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: Retrospective study of the camelford water incident. *BMJ* 1999;319:807-11.
66. Johnson GV, Jope RS. Aluminum alters cyclic AMP and cyclic GMP levels but not presynaptic cholinergic markers in rat brain *in vivo*. *Brain Res* 1987;403:1-6.
67. Chalimoniuk M, Langfort J, Lukacova N, Marsala J. Upregulation of guanylyl cyclase expression and activity in striatum of MPTP-induced parkinsonism in mice. *Biochem Biophys Res Commun* 2004;324:118-26.
68. Tseng KY, Caballero A, Dec A, Cass DK, Simak N, Sunu E, *et al.* Inhibition of striatal soluble guanylyl cyclase-cGMP signaling reverses basal ganglia dysfunction and akinesia in experimental parkinsonism. *PLoS One* 2011;6:e27187.
69. Berry C, La Vecchia C, Nicotera P. Paraquat and Parkinson's disease. *Cell Death Differ* 2010;17:1115-25.
70. Manning-Bog AB, McCormack AL, Li J, Uversky VN, Fink AL, Di Monte DA, *et al.* The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: Paraquat and alpha-synuclein. *J Biol Chem* 2002;277:1641-4.
71. Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. *Brain Res* 1999;823:1-10.
72. Day BJ, Patel M, Calavetta L, Chang LY, Stamler JS. A mechanism of paraquat toxicity involving nitric oxide synthase. *Proc Natl Acad Sci U S A* 1999;96:12760-5.
73. McCormack AL, Thiruchelvam M, Manning-Bog AB, Thiffault C, Langston JW, Cory-Slechta DA, *et al.* Environmental risk factors and Parkinson's disease: Selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol Dis* 2002;10:119-27.
74. Rappold PM, Cui M, Chesser AS, Tibbett J, Grima JC, Duan L, *et al.* Paraquat neurotoxicity is mediated by the dopamine transporter and organic cation transporter-3. *Proc Natl Acad Sci U S A* 2011;108:20766-71.
75. Morán JM, Ortiz-Ortiz MA, Ruiz-Mesa LM, Niso-Santano M, Bravosanpedro JM, Sánchez RG, *et al.* Effect of paraquat exposure on nitric oxide-responsive genes in rat mesencephalic cells. *Nitric Oxide* 2010;23:51-9.
76. Kelner MJ, Bagnell R, Hale B, Alexander NM. Methylene blue competes with paraquat for reduction by flavo-enzymes resulting in decreased superoxide production in the presence of heme proteins. *Arch Biochem Biophys* 1988;262:422-6.
77. Giri SN, Krishna GA. The effect of paraquat on guanylate cyclase activity in relation to morphological changes of guinea pig lungs. *Lung* 1980;157:127-34.
78. Hanafy KA, Martin E, Murad F. CCTeta, a novel soluble guanylyl cyclase-interacting protein. *J Biol Chem* 2004;279:46946-53.