Unraveling the Role of Cyanidin-3-Glucoside as Calcium Channels Blocker: Therapeutic Advancement for Parkinson Disease

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Abstract

The prevalence of neurodegenerative ailments like Parkinson disease is spreading all around the globe is posing threat and an alarming situation for human society. Cyanidin-3-glucoside

being a marvelous polyphenolic candidate who has earned its fame of having multi properties like antioxidant, antitumor, anti-inflammatory and neuro protective as well. According to considerations about pathogenesis of Parkinson disease, mitochondrial dysfunction and oxidative stress is involved in Calcium homeostasis and Calcium channels regulation but exact mechanism related to Calcium channel is not clear. Cyanidin-3-glucoside has been proved itself as a very potent player of performing its activities in maintaining Calcium homeostasis by decreasing oxidative stress, by waning reactive oxygen species and by preventing $Calcium^{+}$induced mitochondrial depolarization. Studies have been done on different models of Parkinson disease on different aspects but effect of C3G to prevent neuronal loss through $Calcium^{+}$ channels in PD is still hidden.

Key words

Cyanidin-3-glucoside, Parkinson disease, Ca^{2+} channels

List of Abbreviation

PD- Parkinson disease

C3G- Cyanidin-3-glucoside

Ca^{2+}- Calcium ion

VGCC- Voltage gated calcium channels

ROS- Reactive oxygen species

BBB- Brain blood barriers

ATP- Adenosine triphosphate

NDs- Neurodegenerative disorders

ER- Endoplasmic reticulum

Zn^{2+}- Zinc ion

Introduction

1. Cyanidin-3-Glucoside (C3G) as A Marvelous Polyphenolic Compound

C3G has membership of flavonoid category of anthocyanin family which is largely found in plant derived foodstuff including colored grains, berries, red cabbages and as well as leafy vegetables and demonstrates protective impacts on various organs. It has widespread series of pharmacological benefits like antioxidant activities, neuro protective effects, gut microbiota variation, metabolic syndrome and antitumor abilities.[1-5] Being a fellow of flavonoid, C3G exhibits splendid anti-inflammatory impacts, anti-carcinogenic ability, antiviral property and anti-aging performances.[6-8] C3G show its great ability in oxidative stress generated disorders by exhibiting prominent anti diabetic and cytoprotective influences.[9] C3G has potential to inhibit ATP stimulated formation of ROS by lowering Ca^{2+} driven mitochondrial depolarization.[10] On energy and along with glucose metabolism, C3G has major antioxidant impacts on tissues.[11] Purple corn extract derived C3G has a variety of pharmacological features in prostate cancer and apoptosis.[12] In hypersensitive rats, C3G play its role in cardiovascular complications and immune system responses.[13] C3G has excellent potential to assist in the upcoming mystery of cytotoxic medicines.[14]

2. Parkinson Disease (PD)

The prevalence of neurodegenerative ailments is spreading all around the globe is posing threat and an alarming situation for human society. It has been proved that metabolites of anthocyanin and anthocyanin also has permission to cross the brain blood barriers (BBB) and hence regulate or monitor various pathways like apoptosis, oxidative stress, specific enzymes and lastly reverse neurodegenerative ailments.[15] PD is recognizes as slowly continuous damage of mesencephalic dopaminergic neurons of the SN (substantia nigra) and striatal projections as well.[16] PD is famous of being second most penetrating neurodegenerative disorder.[17] Occurrence of this notorious disease ranges all around the globe focusing on many factors like genetic predisposition, age, ethnicity, gender and ecological influences.[18] From pathological point of view, Parkinson disorder is pronounced due to loss of dopaminergic neurons in the parse compacta of the SN and by aggregation of irregularly arranged a-synuclein which resides in cytoplasmic inclusions known as Lewy bodies.[19]

Basic classification of PD can be ranked as movements disturbances which can be elaborated by shaking, abnormal walking, slowly movement, stiffness, tremors cognitive disturbance and dementia in progressive step of this disease.[20] Risk of PD are various in different patients under the influence of many kinds of genetic and environmental factors which meet on particular pathways as oxidative stress, neuro inflammation, mitochondrial dysfunction impaired autophagy and protein accumulation.[21]

3. Role of C3G in PD

3.1 C3G and Pathogenesis of PD

With no appropriate therapy and authentic approaches in affected situations, NDs like PD is the most devastating syndrome.[22] PD can be pronounced as prolonged, silently penetrating, neurodegenerative ailment.[23] From pathological aspect of PD, mitochondrial targeted antioxidant agents would be effective candidate to build up therapeutic agents for blocking mitochondrial oxidative loss which is directly involved calcium (Ca^{2+}) regulation. So, in concern with PD, candidate like flavonoids that can hit oxidative stress can be a prominent agent for neuroprotection.[24] C3G as a multifunctional anthocyanin represents antioxidant activity in neuronal cells.[25] C3G defends against amyloid β-generated neuronal cell death by eradicating multiple apoptotic signals.[26]

From developmental and progression related aspect in PD, PINK1 along with PAKIN performs superb active functions in mitochondrial functions which is linked with Ca^{2+} balance and ATP production with the aid of a process known as mitophagy. In case of mutation in PINK, which act as an alarm for mitochondrial damage, cell apoptosis enhances in PD. C3G has been proved itself as antioxidant in PINK and PARKIN signaling pathways.[27-29] Degeneration of dopaminergic neurons in the central nervous system can be characterized as hallmarks of neuropathological domain C3G has been reported to avoid neuronal cell destruction.[30,31] In the central nervous system, by inhibition of neuro inflammation and oxidative damage, C3G exerts protective effects in prevention and cure.[32] C3G prevents ROS production in different brain areas which are essential for process of learning and memory like in hippocampus and cortex to safe the neurons.[33]

4. PD and Ca^{2+} Channels

Ca^{2+} homeostasis can be ranked as molecular pathogenesis of PD.[34] Ca^{2+} balance is main for the integrity of neuronal maintenance as it play key function in synaptic transmission, cell survival and neuronal plasticity. When Ca^{2+} signals activate they trigger a cascade which results increase in Ca^{2+} level inside the cell through Ca^{2+} influx or due to release of Ca^{2+} from intracellular warehouse like endoplasmic reticulum.[35] It is suggested that onset and prolonged continuation in PD is due to conflicts in monitoring of Ca^{2+} control in two neuronal regions. Ca^{2+} homeostasis is monitored by numerous Ca^{2+} channels. In brain problems, neurotoxic impact Ca^{2+} balance in PD has been proved significant in clinical and experimental studies.[36] Dysregulation of Ca^{2+} balance has been interconnected with manifold neurological disease High level of Ca^{2+} in cytoplasm cause increased uptake of mitochondrial Ca^{2+} which is known as potent player in PD.[37] Being a major agent in signaling both pre synaptic and post synaptic phenomena and various cellular outputs, Ca^{2+} undergoes finely exact regulation in neuron.[38] Ca^{2+} signaling recovery is monitored by channel inactivation, sodium calcium transport through membrane which forces the Ca^{2+} to move into endoplasmic reticulum (ER), mitochondria and other warehouses inside the cell mitochondria exhibits prominent part in Ca^{2+} recovery and also deliver fuel to ATP dependent pumps.[39] Post martum studies of PD victims and related experimental models have revealed that neuronal Ca^{2+} control has main role in chronic neurodegenerative disorders.[40] Ca^{2+} signaling provides assistance in multiple functions in cellular world like proliferation, apoptosis, cell excitability, differentiation and contraction actions of cell.[41,42] Inhibition of Ca^{2+} taking from outsider areas of cells is mostly neuroprotective.[43]

4.1 Voltage Gated Calcium Channels in PD

Voltage gated calcium channels (VGCC) performs critical role in in maintain Ca^{2+} homeostasis and controlling and processing of multiple physiological process in neurons. So, disturbance in Ca^{2+} regulation is linked with different types of neurological ailments like PD.[44] VGCC make possible accurate Ca^{2+} homeostasis by directing Ca^{2+} influx.[45] VGCC are main efficient modulator that regulate the release of potent biomolecules like proteins, hormones and neurotransmitters with the aid of Ca^{2+} sensing. Normally VGCC disclose at high voltage and shuts down on slowly during depolarization in the same time Ca^{2+} influx occurs.[46]

Mechanism of disease progression in PD runs via modulator VGCC showing a relationship between alpha synuclein release, neurodegeneration and changes in Ca^{2+} influx.[47]

4.2 L-Type Calcium Channels in PD

PD shows its pathogenesis with key performance of L-type Ca^{2+} channel. Degeneration of dopaminergic neurons is the consequence of alterations in the Ca^{2+} balance due to active expression of efficient L-type channels which depends on performance of UPS (ubiquitin-proteasome system). Enhancement of L-type Ca^{2+} channels expression is linked with lowering down expression of an E3 enzyme (Parkin) of ubiquitin-proteasome system. So link between them may be a source in controlling pathogenesis of PD.[44] Role of VGCC in pace making with assistance of Ca^{2+} influx is very basic in mitochondrial oxidative stress by blocking of L-type Ca^{2+} channels.[34] In neurons, mutant LRKK2 is also a source of increased intracellular Ca^{2+} which ultimately affect L-type VGCC.[43] In this system, Ca^{2+} chelators or blockers of L-type Ca^{2+} channels gives protection as Ca^{2+} discharge through lysosomal stores due to mutant LRRK2.[48] Dopaminergic neurons are under great stress due to their autonomous pace maker system which work with the help of L-type Ca^{2+} channels leads to intracellular Ca^{2+} oscillations.[49] L-type VGCC activation due to Ca^{2+} influx in nigral neurons play main part in pathogenesis of PD.[50] Study was done to explain that Ca^{2+} channel blockers are connected with relatively lower risk of PD in patients with hypertension.[51]

5. Effect of C3G on Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction can be regarded as a prominent player in the development of familial and sporadic forms of PD.[52,56] High level of oxidative stress poses a great impact on cell death and neurotoxicity induction which automatically leads to NDs like PD. And oxidative stress is linked with Ca^{2+} homeostasis and ultimately with mitophagy.[53] Mitochondria can be ranked as chief supplier of neuronal adenosine triphosphate (ATP) hence show critical presentation in brain related energy metabolism. Mitochondria work as Ca^{2+} sinks and we can say that like anabolic factories so necessary for neuronal maintenance and integrity. Neurons are in need of best triggering of mitochondrial activities to ensure their health.[54,55] Furthermore to the conventional role of ATP production, mitochondria can be

renounced as responsible for apoptosis, ROS and Ca^{2+} homeostasis in axonal development and synaptic transmission of action potential in neurons.[56-57]

Cellular destruction and damage is the result of mitochondrial dysfunction and along with oxidative stress due to formation of superoxide and complex 1 which is indispensible for normal function of neurons.[58] Mitochondrial Ca^{2+} homeostasis is affected by alterations in the quantity and activity of ER-mitochondrial linking sites and this event is organized by Parkin which is hallmarks of PD.[59-60] C3G can be proved itself as a Ca^{2+} channel blocker by enhancing ATP induced Ca^{2+} increase, phenomena of mitochondrial depolarization and surprising formation of reactive oxygen species C3G performs a key part in blocking various pathways involved in ATP induced Ca^{2+} signaling and release of Ca^{2+} from intracellular warehouse.[10] Therefore, C3G as a Ca^{2+} channel blocker can be used in Ca^{2+} channels related pathway in PD.

6. Effect of C3G on Excitotoxicity

From pathological point of view, excitotoxicity is another one fundamental pathway in PD and glutamate is the chief excitatory neurotransmitter of the central nervous system which monitors learning, memory, motor functions and as well as development of neurons. Excessive discharge of glutamate is directly linked with neuronal loss. In PD, high level of glutamate dependent excitotoxicity causes mental and motor dysfunction leads to neuronal death. Glutamate generated intracellular Ca^{2+} rise, reactive oxygen species formation, mitochondrial disturbances and osmotic inflammation of neurons.[36]

So much increase in Ca^{2+} of mitochondrial due to high glutamate stimulated Ca^{2+} triggers formation of ROS which leads to cell death. C3G has potential to reduce glutamate generated [Zn^{2+}] from outsider resources by minimizing mitochondrial depolarization and generation of reactive oxygen species which is beneficial in neuroprotection alongside glutamate induced cell death.[61-63] Previous study evaluate that C3G, exerts its direct neurotoxicity and, its ability to protect brain neurons from oxidative damage.[64] So, prevention of glutamate outflowing is considered an essential neuroprotective procedure and a promising target for evolving new therapeutic approaches.

7. Effect of C3G on PD Models through Ca^{2+} Channels

Previous investigations proved that anthocyanin may be a source of efficient dietary supplement to defend against neurodegenerative diseases.[15] Flavonoids can be regarded as having capacity to block numerous ion channels.[10] It has been explored that impacts of anthocyanin on metabolism and mitochondria that have ability of unique health defending methods and alterations in mitochondrial events, cellular redox signaling phenomena take part in prolonged processes of numerous pathological situations, including cancer, diabetes, cardiovascular and neurodegenerative problems.[65]

Transgenic PD mice (C57BL/6 mice) received grape polyphenol concentrate (1.5 mL/kg/day) from the age of 6–8 weeks for four months have improved their behavioral and mental activities. Grape polyphenol exhibits neuroprotective activity by reducing the α-synuclein accumulation in the frontal cortex and neuroinflammatory response in the frontal cortex and hippocampus. [66] Therapeutic effect of 2- (2 Thienyl) Benzothiazoline was assessed against rotenone-induced PD in rats.[17] C3G could protect 1-methyl-4-phenyl-1,2,3,6− tetrahydropy ridine (MPTP)-induced PD mice. Pharmacodynamic study of C3G in PD mice was based on gut to brain hypothesis.[67]

PD has multipath pathogenesis hence have multiple mechanism of pathogenesis hence there are manifolds method for treatment and cure for eradication of this disease. One mechanism is Ca^{2+} channel regulation and control which is not so much explored yet in PD. Different plant based treatments are used currently. Polyphenolic compounds are so much famous for their multiple therapeutic effects. C3G is excellent candidate has neuroprotective effect and is hot topic of research these days and being used in different aspects of PD models. But role of C3G in PD models through Ca^{2+} channels is still in need to be investigated. No doubt this research will open a new window for clinical and therapeutic approaches for treatment and cure of this day by day spreading PD.

Conclusion

PD can be characterized as a popular neurodegenerative disorder in the central nervous system with no appropriate therapeutic approaches. According to pathogenesis of PD, C3G may be a great neuroprotective agent or antioxidant candidate by monitoring and regulating

Ca^2channels. Studies have been done on different models of Parkinson disease on different aspects but gap of these studies has been shown by this review that effect of C3G on PD to protect neuronal damage through Ca^2 channels is in need to be explored.

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