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Review

Green tea catechins as brain-permeable, natural iron chelators-antioxidants for the treatment of neurodegenerative disorders

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Neurodegeneration in Parkinson's, Alzheimer's, or other neurodegenerative diseases appears to be multifactorial, where a complex set of toxic reactions, including oxidative stress (OS), inflammation, reduced expression of trophic factors, and accumulation of protein aggregates, lead to the demise of neurons. One of the prominent pathological features is the abnormal accumulation of iron on top of the dying neurons and in the surrounding microglia. The capacity of free iron to enhance and promote the generation of toxic reactive oxygen radicals has been discussed numerous times. The observations that iron induces aggregation of inert α-synuclein and beta-amyloid peptides to toxic aggregates have reinforced the critical role of iron in OS-induced pathogenesis of neurodegeneration, supporting the notion that a combination of iron chelation and antioxidant therapy may be one significant approach for neuroprotection. Tea flavonoids (catechins) have been reported to possess divalent metal chelating, antioxidant, and anti-inflammatory activities, to penetrate the brain barrier and to protect neuronal death in a wide array of cellular and animal models of neurological diseases. This review aims to shed light on the multipharmacological neuroprotective activities of green tea catechins with special emphasis on their brain-permeable, nontoxic, transitional metal (iron and copper)-chelatable/radical scavenger properties.

Keywords: (–)-epigallocatechin-3-gallate / Flavonoid / Hypoxia / Neurodegeneration / Parkinson's disease

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1 Introduction

The consumption of tea (*Camellia sinensis*) is believed to have been initiated five thousands years ago in China and India. Tea is commonly associated with traditional beverage rituals and particular lifestyles, especially in Japan, China, India, and England; nevertheless, nowadays it is considered as a source of dietary constituents endowed with biological and pharmacological activities with potential benefits to human health. Indeed, it is the novel pharmacological activities that are arousing interest in their possible clinical use for prevention and therapeutics in several diseases. Several of these are subject, in the last few years, to intensive investigation in diverse medical disciplines, such as cardiology, oncology, inflammatory diseases, and neurology [1–3]. The favorable properties of green tea (GT) extract have been ascribed to their high content of polyphenolic flavonoids. Fresh tea leaves contains a high amount of catechins, a group of flavonoids or flavanols, known to constitute 30–45% of the solid GT extract [4, 5]. Catechin polyphenols have been demonstrated to act directly as radical scavengers of oxygen and nitrogen species and exert indirect antioxidant effects through activation of transcription factors and antioxidant enzymes, thus modulating the cellular redox state (see reviews: [1, 6, 7]. In addition to their radical-scavenging action, GT catechins possess well-established metal-chelating properties. Structurally important features defining their chelating potential are the 3′,4′-dihydroxyl group in the B ring [8], as well as the gallate group [9, 10], which may neutralize ferric iron to form redox-inactive iron, thereby protecting cells against oxidative damage [11].

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Abbreviations: **Aβ**, amyloid beta; **AD**, Alzheimer's disease; **APP**, amyloid precursor protein; **DFO**, desferrioxamine; **EGCG**, (–)-epigallocatechin-3-gallate; **HIF-1**, hypoxia inducible factor-1; **IRE**, iron responsive element; **IRP**, iron regulatory protein; **OS**, oxidative stress; **PD**, Parkinson's disease; **PKC**, protein kinase C; **sAPPα**, soluble APP-alpha; **SN**, substantia nigra

The importance of polyphenolic flavonoids in enhancing cell resistance to oxidative stress (OS) goes beyond the simple scavenging activity and is mostly interesting in those pathologies where OS plays an important role, such as in neurodegenerative diseases and aging. Aging is characterized by decrements in tissue function and accumulation of mitochondrial DNA mutations, particularly in the brain that contains postmitotic cells. Many lines of evidence suggest that iron-mediated OS resulting in reactive oxygen species (ROS) generation and inflammation plays a pivotal role in the age-associated cognitive decline and neuronal loss in neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's diseases (AD, PD, and HD, respectively). Transitional metal alterations (*e.g.*, iron, copper, and zinc) have been described in brains of Parkinsonian patients and of other neurodegenerative diseases, which may be caused, to a large degree, by endogenous dysregulation of iron uptake, transport, distribution, and storage [12, 13]. The redox-active metals are promoters of membrane-associated OS including lipid peroxidation and oxidative modifications of membranes and their coupled proteins, such as receptors. Dietary metals may influence the risk of PD, AD, and other neurodegenerative disorders [14], while persistent iron deprivation has been shown to protect cortex and hippocampal cells from kainate-induced damage [15]. Furthermore, neurochemical and genomics studies in PD, and more recently in AD, have provided evidence for the involvement of supplementary processes, including glutamatergic neurotoxicity, nitric oxide elevation, dysfunction of ubiquitin-proteasome system, and mitochondria, which may lead to breakdown of energy metabolism and consecutive intraneuronal calcium overload, increased expression of apoptotic proteins, and loss of tissue reduced glutathione (GSH, an essential factor for removal of hydrogen peroxide) [12, 16–22]. These series of neurotoxic events may act independently or cooperatively, leading eventually to the demise of the neurons. Thus, considering the multifactorial nature of neurodegenerative disorders, drugs directed against a single target will be ineffective and rather a single drug or cocktail of drugs with pluripharmacological properties may be more suitable to be employed.

One innovative therapeutic approach could be the use of nontoxic, brain-permeable natural plant polyphenol flavonoids, reported to possess multifunctional activities, being iron chelators, radical scavengers, anti-inflammators, and neuroprotectants [6, 8, 9, 23, 24] as reviewed in [25, 26]. Research from our laboratory has demonstrated that the antioxidant-iron chelating activity of the major GT polyphenol (–)-epigallocatechin-3-gallate (EGCG) plays a major role in the prevention of neurodegeneration in a variety of cellular and animal models of neurodegenerative diseases [27, 28]. Furthermore, collective studies indicated that beyond this property, catechin flavonoids regulate various signaling pathways involved in cellular survival, growth, and differentiation as protein kinase C (PKC) and extracellular mitogen-activated protein kinase (MAPK) [26, 29] and promotion of neurite outgrowth [30]. In addition, EGCG was shown to down-regulate proapoptotic genes, such as bad, bax, mdm2, caspase-1, cyclin-dependent kinase inhibitor p21, and TNF-related apoptosis-inducing ligand (TRAIL) [31, 32], and to regulate transcriptional activation [1, 7, 33–35]. These findings suggest that GT extract may be a source of neuroprotectants, with particular relevance to neurodegenerative diseases where OS has also been implicated.

2 GT catechins as brain-permeable, nontoxic iron chelators to "iron out" iron from the brain

One of the major pathology of progressive neurodegenerative diseases is the accumulation of iron in the degenerating neurons [36]. Various metals have been implicated in the pathophysiology of certain neuropsychiatric diseases – copper and iron in Wilson's disease; aluminum, zinc, and iron in AD; iron in PD, Friedreich's ataxia, and Hallervorden-Spatz-syndrome, just to mention a few [37–39]. Studies on human and animal brains have shown that the distribution of brain iron is uneven as compared to other metals. Thus, iron is present in substantia nigra (SN), globus pallidus, and dentate gyrus at a concentration equal to or greater than that found in the liver. These three brain regions are known to be associated with neurodegenerative diseases [40]. Redox-active iron has been observed in the peripheral halo of Lewy body (LB), the morphological hallmark of PD, also composed of lipids, aggregated α-synuclein (concentrating in the rim of LB), and ubiquitinated, hyperphosphorylated neurofilament proteins [41]. α-synuclein associated with presynaptic membrane is not toxic; however, a number of recent studies [42–44] have shown that it forms toxic aggregates in the presence of iron and this is considered to contribute to the formation of LB *via* OS. In AD, changes in the levels of iron, ferritin, and transferrin receptor (TfR) have been reported in the hippocampus and cerebral cortex [45–47]. Iron promotes both deposition of amyloid beta (Aβ) peptides and induction of OS, which is associated with the cerebral amyloid-containing plaques. Indeed, it has been demonstrated that amyloid deposits are enriched with zinc, iron, and copper [39]. Recently, redox-active iron bound to ribosomes was demonstrated to oxidize ribosomal RNA in AD [45]. In addition, iron may contribute to AD *via* regulation of amyloid precursor protein (APP) translation, resulting from the existence of an iron-responsive element (IRE-type II) in the 5′UTR region of APP mRNA [48]. This is consistent with biochemical evidence pointing to APP as a redox-active metalloprotein [49].

The involvement of metals in protein deposition in neurological disorders has encouraged the development of iron

chelators as a major new therapeutic strategy. Metal chelation has the potential to prevent iron-induced ROS, OS, and aggregation of α-synuclein and Aβ. Indeed, the limited number of neuroprotective studies that have been carried out so far indicate that iron-chelation therapy could be a viable neuroprotective approach for neurodegenerative disorders [50–52]. Animal studies have shown neuroprotective activity of the prototype iron chelator drug desferrioxamine (DFO) and the antibiotic iron and copper chelator 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol) against the neurotoxins 6-hydroxydopamine (6-OHDA) and *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity in mice [53, 54]. However, DFO is a very poor brain penetrating agent and clioquinol is highly toxic [55]. More recently, the multifunctional iron chelator-monoamine oxidase (MAO) A and B inhibitor, brain-permeable compound, M-30, showed neuroprotective activities in neuronal rat PC12 and P19 cell cultures against serum deprivation, 6-OHDA [56, 57] and in MPTP-induced parkinsonism [58].

The ability of GT polyphenols to act as metal chelators [9–11] and to have access to the brain makes them a novel promising therapeutic approach for treating AD, PD, and amyotrophic lateral sclerosis (ALS), in which accumulation of iron has been found [12, 36, 59]. Ionic iron participates in Fenton chemistry, generating cytotoxic oxygen radicals, the most potent being the hydroxyl radical that is particularly reactive with lipid membranes. Many *in vitro* studies have clearly demonstrated the potent peroxyl radical-scavenging abilities of GT polyphenols in preventing oxidation of lipid membranes and low-density lipoproteins (LDL). Ingestion of either black tea or GT extracts protected plasma LDL oxidation in humans [60] and in rats fed with GT extract [61]. GT and black tea extracts were shown to strongly inhibit lipid peroxidation promoted by iron-ascorbate in homogenates of brain mitochondrial membranes [62]. A similar effect was also reported using brain synaptosomes, in which the four major polyphenol catechines of GT were shown to inhibit iron-induced lipid peroxidation [9]. In the majority of these studies, EGCG was shown to be more efficient as a radical scavenger than its counterparts ECG, EC, and EGC, which might be attributed to the presence of the trihydroxyl group on the B ring and the gallate moiety at the 3′ position in the C ring. [63]. In our hands, EGCG displayed iron-chelating potency similar to that of DFO and of our newly developed nontoxic, lipophilic, brain-permeable iron chelator drug, VK-28 (Fig. 1). Thus, the cytoprotective effect of tea polyphenols against lipid peroxidation may reflect a combination of a direct scavenging of oxygen, nitrogen, and lipid radicals, as well as iron chelation.

3 EGCG regulates APP generation/ processing and Aβ formation

The capacity of catechins to neutralize excess of free iron may have a direct implication to AD, which is inherent primarily, to the nature of APP as an iron-regulated protein [48, 64]. APP is post-transcriptionally regulated by iron regulatory proteins (IRPs), which are labile iron pool-sensitive cytosolic RNA proteins, binding specifically to the IREs located in the 5′ or 3′ untranslated regions of iron metabolism-associated mRNAs. Thus, reduction of the free-iron pool by EGCG chelation may lead to suppression of APP mRNA translation, by targeting the IRE-II sequences in the APP 5′ UTR [48], as was recently shown for DFO and the bifunctional amyloid-binding/metal-chelating drug XH1 [65] (Fig. 2). In accordance, our recent studies have shown that prolonged administration of EGCG to mice induced a reduction in holo-APP levels in the hippocampus [66]. This is supported by the ability of EGCG to induce a significant down-regulation of membrane-associated holo-APP levels in neuroblastoma SH-SY5Y cells (Fig. 3), an effect that was accompanied by a concomitant decrease in Aβ levels, similar to the novel iron chelator M30, a VK-28 series derivative (submitted for publication). Furthermore, wine and GT polyphenols are able to inhibit formation, extension, and destabilization of Aβ fibrils [67], and to protect against Aβ-induced neurotoxicity [66]. Attenuation of APP synthesis and consequential Aβ production by EGCG could be of therapeutic value for AD therapy, as increased generation of Aβ plays a central role in AD plaque formation [68]. Indeed, overexpression of mutant human APP gene in transgenic mice was found to produce excessive Aβ, cerebral amyloid deposition, and an Alzheimer-like pathology [69]. The increased promotion of holo-APP expression after ischemia, hyperglycemia, traumatic brain injury, and cellular energy depletion have been shown to route the APP metabolism from the nonamyloidogenic to the amyloidogenic pathway [70–74].

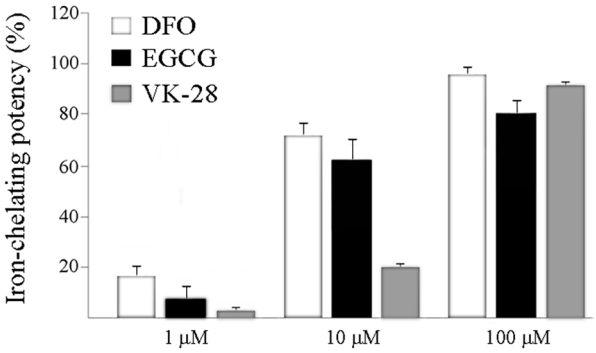

Figure 1. Iron-chelating activity of EGCG, VK-28, and DFO on Fe(II). Comparative analysis of the Fe(II) chelating potency of EGCG, VK-28, and DFO was performed, assessing their ability to compete with ferrozine for the ferrous ions and further ferrous ferrozine complexes formation, thereby resulting in a decrease in the absorbance at 562 nm. Drugs were mixed with 50 μM ferrozine in 5% ammonium acetate (pH 7) followed by the addition of 10 μM Fe_2SO_4 for 2 h. Percentage of the chelating effect was calculated using the following equation: [1–(absorbance of sample at 562 nm)/(absorbance of control, without drugs, at 562 nm)] × 100.

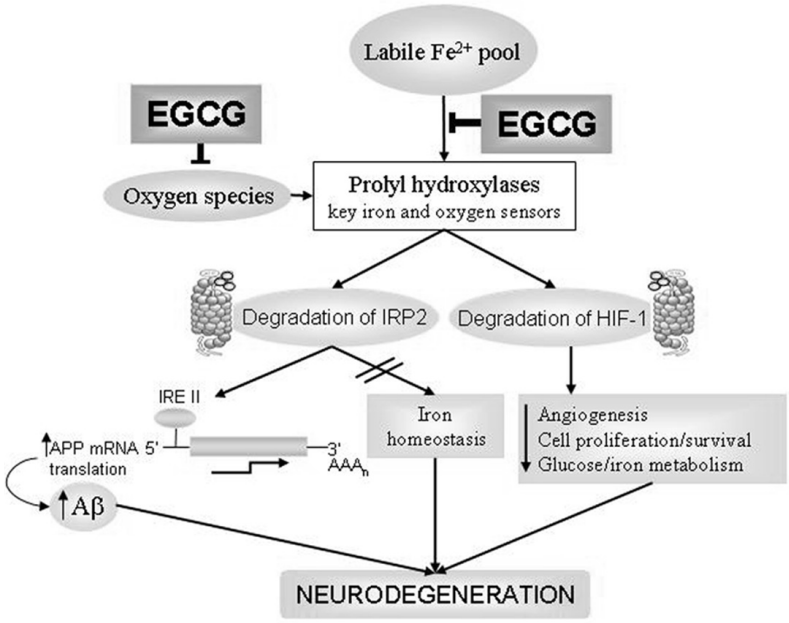

Figure 2. Iron-induced neurodegeneration in AD *via* transcriptional activation of APP mRNA and suppression of hypoxia-inducible genes. Increase in labile Fe^{2+} pool can elevate the production of APP *via* proteasomal-mediated inactivation of IRP2, thereby promoting the translation of APP mRNA from its 5′UTR-typeII). Increased iron and oxygen species may activate the prolyl hydroxylase enzymes, which are key iron and oxygen sensors, leading to proteasomal-mediated degradation of the transcription factor HIF-1 a master regulator orchestrating the coordinated induction of a wide array of survival genes. It has been suggested that IRP2, similar to HIF-1, can be enzymatically modified by a prolyl hydroxylase, routing it to proteasomal degradation. Both iron chelation and oxygen species scavenging by EGCG may prevent the degradation of IRP2 and HIF-1, resulting in the promotion of cell survival processes such as angiogenesis, glucose metabolism and maintenance of iron homeostasis. EGCG, IRP, HIF-1. Sharp arrows indicate positive inputs, whereas blunt arrows are for inhibitory inputs. For a more detailed explanation read text.

The other important pharmacological action of EGCG is related to the recent observation that EGCG promotes the generation of the soluble N-terminal fragment, soluble APP-alpha (sAPPα), *via* PKC-dependent activation of the enzyme α-secretase, thereby increasing the production of the nontoxic sAPPα [66] (Fig. 3). This is supported by the ability of EGCG to up-regulate PKCα and PKCε isoforms in mice striatum and hippocampus [27, 66]. Since sAPPα and Aβ are formed by two mutually exclusive mechanisms, stimulation of the secretory processing of sAPPα might prevent the formation of the amyloidogenic Aβ. Thus, EGCG may influence Aβ levels, either *via* translational inhibition of APP or by stimulating sAPPα secretion (Fig. 4). Cleavage of APP within the Aβ domain by α-secretases is of physiological interest, not only because it precludes the formation of Aβ, but also because it promotes the generation of sAPPα that exhibits neuroprotective properties [75, 76]. A number of reports supported the notion that promotion of α-secretase-mediated APP processing, rather than down-regulation of Aβ production, might offer another approach to AD treatment [77].

4 GT catechins and induction of iron/ hypoxia-responsive genes

The chelation of iron affects not only the post-transcriptional regulation of iron homeostasis-related mRNAs (*e.g.*, TfR, ferritin), but also the induction of genes regulated by the transcription factor hypoxia inducible factor-1 (HIF-1), a master regulator orchestrating the coordinated induction of an array of genes sensitive to hypoxia [78]. The target genes of HIF are especially related to angiogenesis, cell proliferation/survival, and glucose/iron metabolism [79]. In this context, iron was recently shown to overcome HIF-1 activation by the GT catechins, EGCG and epicatechin-3-gallate (ECG), as well as by DFO [34, 35]. In fact, both HIF-1 and IRP2 share a common iron-dependent proteasomal degradation pathway, by the action of key iron and oxygen sensors prolyl hydroxylases, which become inactivated by iron chelation [80, 81]. Thus, the reduction in the free-iron pool by EGCG chelation may result in the inhibition of prolyl hydroxylases and consequently, in the concerted activation of both HIF and IRP2. As IRPs and HIF-1 coordinate the expression of a wide array of genes involved in cellular iron and glucose homeostasis, survival and proliferation [78, 82], their activation could be of major importance in neurodegenerative diseases (for a detailed explanation see Fig. 2).

5 Conclusions

The multifactorial nature of neurodegenerative diseases makes the use of compounds with polypharmacological activities or cocktail of drugs, a promising therapeutic approach for the treatment of these disorders, as practiced in the management of other diseases such as AIDS, ischemia, cancer, and neurotrauma. A wealth of new data suggests that GT catechins may well fulfill the requirements for a putative neuroprotective drug having diverse pharmacological activities. Ordinarily viewed as simple radical

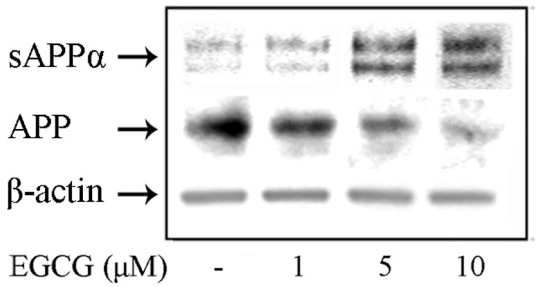

Figure 3. Effect of EGCG on APP protein and sAPPα release. SH-SY5Y cells were incubated without or with increasing concentrations of EGCG (1–10 μM) for 2 days, and then APP and sAPPα were evaluated in the cell lysate and medium, respectively, by Western blot analysis. mAb against the APP N-terminus (22C11) was used for APP detection, whereas mAb recognizing an epitope within residues 1–17 of Aβ domain of APP (6E10) was employed for sAPPα determination.

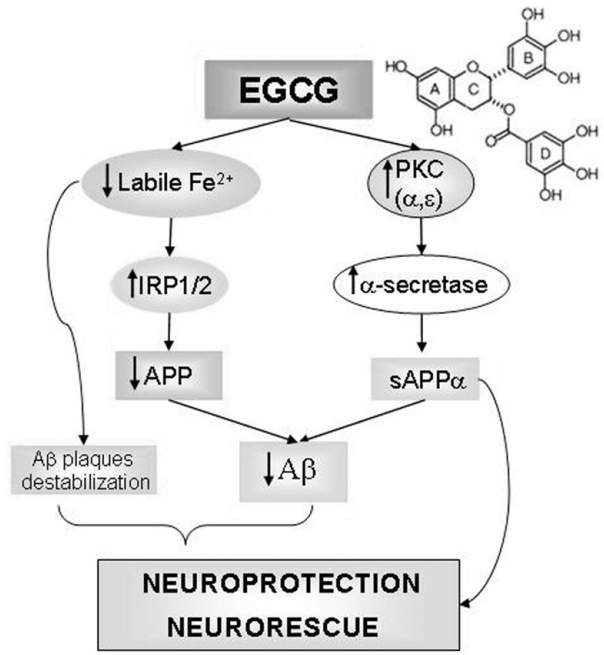

Figure 4. Proposed schematic model for EGCG neuroprotective/neurorescue effects *via* regulation of APP processing and Aβ formation. ↑, increased levels/activity; ↓ decreased levels/activity. For full explanation see text.

scavengers, GT catechin polyphenols are considered at present to invoke a spectrum of cellular mechanisms of action related to their neuroprotection/neurorescue activities. Recently, a new dimension was added to these actions, associated with the iron-chelating property of GT catechins and the impact on neurodegenerative processes, as oxidative chain breakers and inhibitors of protein aggregation and Aβ plaque formation. Thus, GT catechins may be recognized as multifunctional, brain-permeable iron chelators that can prevent or delay neuronal death in the degenerating human brain [64]. Being of natural origin, they may not exert toxic side effects inherent to synthetic drugs.

6 References

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