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REVIEW ARTICLE

Targeting polyamines and biogenic amines by green tea epigallocatechin-3-gallate

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Abstract Biogenic amines and polyamines are organic polycations derived from aromatic or cationic amino acids. They exert pleiotropic effects, more related to intercellular communication in the case of biogenic amines, and to intracellular signaling in the case of polyamines. The bioactive compound epigallocatechin-3-gallate (EGCG), a major component of green tea, has been shown to target key enzyme of biogenic amine and polyamine metabolic pathways. Herein, we review the specific effects of EGCG on concrete molecular targets of both biogenic amine and polyamine metabolic pathways, and discuss the relevance of these data to support the potential therapeutic interest of this compound.

Keywords Polyamine · ODC · SSAT · DDC · HDC · Histamine · EGCG · Tea

Abbreviations

EC	Epicatechin
ECG	Epicatechin-3-gallate
EGC	Epigallocatechin
EGCG	Epigallocatechin-3-gallate
DDC	Dopa decarboxylase
HDC	Histidine decarboxylase
MCP-1	Monocyte chemoattractant protein 1
ODC	Ornithine decarboxylase
SAMDC	S-adenosyl methionine decarboxylase
SSAT	Spermidine/spermine N-acetyl transferase

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Introduction

Tea is the second beverage most consumed in the world after water. It is a product made up from leaves and buds of *Camellia sinensis*. Tea consumption is part of many people's daily routine, as an everyday drink and as a therapeutic aid in many illnesses. There are different types of tea depending on manufacturing process: white tea is the uncured and unfermented tea leaf, green tea is 'non-fermented', oolong tea is 'semi-fermented' and back or red tea is 'post-harvested fermented' before drying and steaming. Chinese have known about the medicinal benefits of green tea since ancient times, using it for treatment of headaches, body aches and pains, digestion, depression, detoxification, as an energizer and, in general, to prolong life. In recent years, the legendary medicinal properties of tea have been given serious scientific support.

Tea is a natural source of the amino acid theanine, methylxanthines such as caffeine and theobromine and polyphenolic antioxidant. Polyphenols constitute of the most interesting group of green tea components and green tea can be considered as an important source of polyphenols, particulary flavonoids. The main flavonoids present in green tea are catechins (flavans-3-ols). There are four major catechins: (-)-epigallocatechin-3-gallate (EGCG, approximately 59% of total catechins), (-)-epigallocatechin (EGC, 19% approximately), (-)-epicatechin-3-gallate (ECG, 13.6% approximately), and (-)-epicatechin (EC,

6.4% approximately) (Cabrera et al. 2006). These polyphenols are antioxidant in nature and have been shown to function as anti-inflammatory and anti-carcinogenic agents in various biological systems (Katiyar and Mukhtar 1997; Tipoe et al. 2007). EGCG, the most abundant polyphenol in green tea leaves, is believed to be the most responsible compound for the health benefits attributed to tea (Graham 1992).

Several studies showed that EGCG induces apoptosis and cell cycle arrest in tumor cells (Gupta et al. 2003; Roy et al. 2005), inhibits urokinase activity (Jankun et al. 1997), matrix metalloproteinases and urokinase-plasminogen activator (Ho et al. 2007), lipoxygenase and cyclooxygenase activities (Hong et al. 2001; Peng et al. 2006), the expression of angiogenesis related genes (Melgarejo et al. 2007), and cell proliferation (Albrecht et al. 2008; Kuo and Lin 2003).

Evidence is accumulating pointing to polyamine and biogenic amine metabolism as key targets for EGCG. In this point, it should be stressed that many reports give support to the observation that positive effects result from the combined action of different catechins. However, the focused aim of this work is to review the current state of knowledge concerning the modulatory actions of EGCG on polyamine and biogenic amine metabolism.

Pleiotropic effects of polyamine and biogenic amines: the metabolic connection

Polyamines (putrescine, spermidine and spermine) are aliphatic polycations derived from arginine/ornithine and methionine metabolism. Their ubiquity and conservation across evolution point to their importance for cell biology. In fact, polyamines have pleiotropic effects with relevant regulatory roles in macromolecular synthesis and cell proliferation rates (Cohen 1998). On the other hand, biogenic amines are also derived from amino acid metabolism and they are mainly related to intercellular communication (Medina et al. 2003). Therefore, both biogenic amines and polyamines exhibit similar biochemical origins for different physiological missions. Some kind of cross-talks among them should be expected and, indeed, this seems to be the case (Chaves et al. 2007; Fajardo et al. 2001a, b; García-Faroldi et al. 2009; Medina et al. 2003).

The diversity of effects of polyamines and biogenic amines points to their involvement in a great variety of diseases when their metabolism is altered (Casero and Pegg 2009; Correa-Fiz et al. 2009; Medina et al. 2003). A deeper knowledge of polyamine and biogenic amine metabolic regulation requires an integration of information concerning their sources and drains, including transport processes (Fajardo et al. 2001b; Paz et al. 2001). Since metabolic deregulation of polyamine and biogenic amine metabolism is connected to plenty of pathological situations, the identification of compounds able to target these processes could open new ways of therapeutical and/or pharmacological intervention. More comprehensive and systemic studies integrating molecular biology, biophysical and bioinformatics tools, as well as "-omics" and systems biology approaches, could contribute to accelerate the advances in this research area (Medina et al. 2005; Montañez et al. 2007).

In the meantime, several alternative approaches have shown that EGCG is a single bioactive natural compound able to target simultaneously several key components of polyamines and biogenic amines metabolism.

EGCG is an irreversible inhibitor of Dopa decarboxylase

Dopa decarboxylase, DDC, is a key enzyme involved in the biosynthesis of biogenic amines. Its primary catalytic activity consists in the conversion of L-Dopa and L-5-hydroxytryptophan into dopamine and serotonin, respectively. Both dopamine and serotonin are key mediators in neurotransmission and their metabolic deregulation is related with prevalent pathologies such as Parkinson's disease and depression (Brotchie and Fitzer-Attas 2009; Cowen 2008).

Some years ago, Voltattorni's group elegantly demonstrated that EGCG (and also epigallocatechin, EGC) is able to inactivate DDC in both a time- and concentration-dependent manner (Bertoldi et al. 2001). This inactivation followed a pseudo-first order kinetic behavior at each fixed concentration of EGCG, with a binding step prior to inactivation. This work showed that EGCG interacts with and binds to the enzyme, presumably in close proximity to the PLP-binding site, leading to irreversible inhibition of DDC.

Effects of EGCG on histamine metabolism

Histamine is a biogenic amine with a major role in different physiological function such the contraction of smooth muscles, increase in vascular permeability, stimulation of gastric acid secretion, neurotransmission, immunomodulation, proliferation, etc., (Beaven 1978; Brown and Roberts 2001). Among all the cell types of the human body, only a few cell types are able to produce histamine. They include some neurons, enterochromaffin-like cells, gastrin containing cells, mast cells, basophils and monocytes/macrophages, among others.

Mast cell-produced histamine is a key mediator of allergic and inflammatory responses. This biogenic amine is produced in a reaction catalyzed by histidine decarboxylase, HDC (Medina et al. 2003), an enzyme extensively studied by our group (Moya-García et al. 2005, 2008, 2009; Olmo et al. 2000, 2002; Rodríguez-Caso et al. 2003a). EGCG targets histamine at two levels. On one hand, EGCG has been shown to inhibit mast cell degranulation (Yamashita et al. 2000). On the other hand, our group first demonstrated a potent inhibitory effect of EGCG on HDC activity (Rodríguez-Caso et al. 2003b). This inhibitory effect was proved by a double approach, namely, UV–Vis spectra of enzyme-bound pyridoxal-5′-phosphate and enzyme activity measurements. Upon treatment with 0.1 mM EGCG, the typical spectrum of the internal aldimine form of pyridoxal-5′-phosphate linked to the apoenzyme shifted to a stable major maximum at 345 nm. This change was very similar to the previously described effects of EGCG on the spectrum of DDC, where a maximum at 420 nm decreased and a maximum at 335 shifted up to 342 nm in the presence of 0.1 mM EGCG (Bertoldi et al. 2001). On the other hand, we showed that EGCG produces a remarkable inhibition (by more than 60%) of purified recombinant rat HDC activity. Furthermore, HDC activity naturally occurring in rat RBL-2H3 basophilic cells was also inhibited by EGCG to a similar degree. Recently, our results have been confirmed by an independent study showing that, in fact, among 22 tested food components, EGCG (along with epicatechin gallate) was the most effective inhibitor of HDC (Nitta et al. 2007).

A recent functional genomics study carried out by our group has shown that, among others, EGCG reduces the expression of the integrins $\alpha 5$ and $\beta 3$ in mast cells (the major histamine-producers of the human body), as well as that of the chemokine monocyte chemoattractant protein 1 (MCP-1), giving rise to a lower adhesion and migration of mast cells, associated with a decreased potential to produce signals eliciting monocyte recruitment (Melgarejo et al. 2007).

Effects of EGCG on polyamine metabolism

The structure of the polyamine metabolic pathway consists of a bi-cycle with two required entrances (ornithine, produced from arginine, and S-adenosylmethionine, produced from methionine) and several alternative exits. The key enzymes of the whole pathway are ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (SAMDC) in the biosynthetic branch and spermidine/spermine acetyltransferase (SSAT) in the catabolic branch (Urdiales et al. 2001). The key features of the whole pathway have been captured in the first mathematical model of mammalian polyamine metabolism (Rodríguez-Caso et al. 2006). We have also modeled arginine catabolism as a source of polyamines (Montañez et al. 2008).

Two out of the three key enzymes of polyamine metabolism have been shown to be targets for EGCG action, namely, ODC and SSAT. ODC catalyzes the conversion of ornithine into putrescine and is considered to be the major rate-limiting step in the biosynthesis of polyamines. In 2002, Bachrach and Wang carried out a critical review of the preceding published research studies showing an inhibitory effect of EGCG on ODC activity in a variety of model systems (Bachrach and Wang 2002). The same authors had devoted an article to the specific anti-cancer activity of EGCG (Wang and Bachrach 2002). In this context, it should be mentioned that Flamigni's group demonstrated that green tea extracts can promote ODC induction in a tumor cell line (Facchini et al. 2003). Recently, other published studies have been added to the evidence pointing to the interfering effects of EGCG on polyamine metabolism. Two of these new studies seem to be particularly relevant. The first one is a study mainly devoted to the effects of resveratrol on polyamine metabolism in human colonic adenocarcinoma cell line Caco-2 (Wolter et al. 2003). This work also shows that EGCG has no effect on SAMDC activity but has at the same time an inhibitory effect on ODC activity and an enhancing effect on SSAT activity. The second study, carried out by Gilmour's group, suggest a potential chemopreventive effect of EGCG in individuals with early, pre-neoplastic stages of cancer having higher levels of polyamines. This group used an ODC/Ras double transgenic model to show that administration of EGCG in the drinking water significantly decreased both tumor number and tumor burden compared with untreated double transgenic mice (Paul et al. 2005).

Pathobiological relevance and future prospect

There is increasing evidence pointing to the beneficial effects of EGCG. They include its neuroprotective and radio-protective actions, its potent inhibitory effect on cytokine and chemokine release, its molecular targets leading to monocyte apoptosis, mast cell degranulation inhibition, as well as its interference with mast cell adhesiveness, migration and monocyte recruitment. All these effects point to EGCG as a highly promising agent with potential pharmacological interest to be evaluated in clinical trials. In this work, we have reviewed the known effects of EGCG on polyamine and biogenic amine metabolism, targeting four key enzymes: three decarboxylases, namely, DDC, HDC and ODC are strongly inhibited in their activities by EGCG, while SSAT activity is increased in the presence of EGCG (Fig. 1). Two lines of

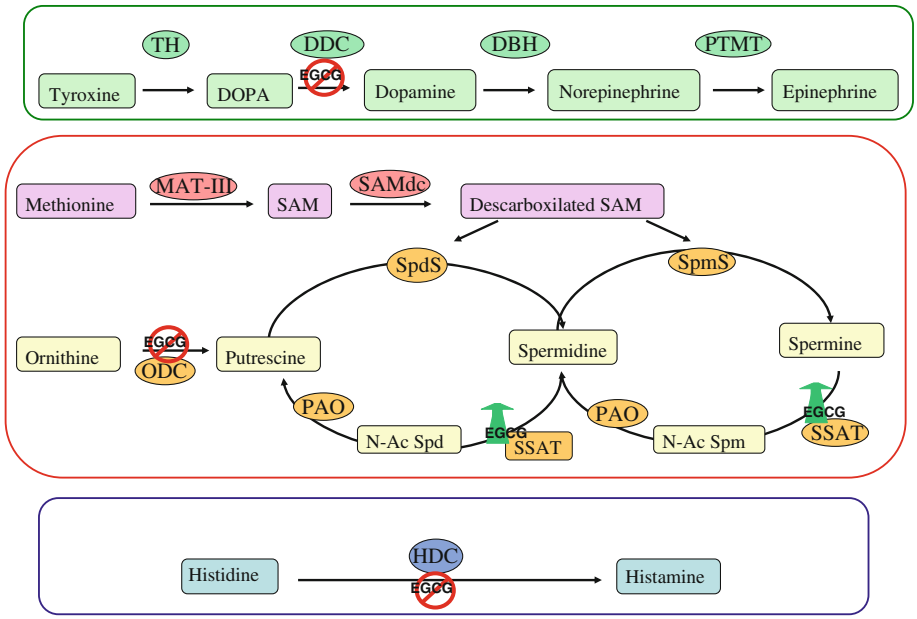

Fig. 1 Scheme of the metabolism of polyamines, histamine and other biogenic amines, showing the effects of epigallocatechin-3-gallate (EGCG) on ornithine decarboxylase (ODC), dopa decarboxylase (DDC), histamine decarboxylase (HDC) and spermidine/spermine acetyltransferase (SSAT) activity. *PAO* Polyamine oxidase; *SpdS* spermidine synthase; *SpmS* spermine synthase; *MAT* methionine adenosyltransferase; *SAMdc* S-adenosylmethionine decarboxylase

research for the near future are suggested. On the one hand, systemic studies such as our recent functional genomics contribution (Melgarejo et al. 2007) could contribute to identify new connected targets for EGCG pharmacological action (Melgarejo et al. 2009). On the other hand, chemical synthesis and combinatorial chemistry could contribute to obtain new EGCG derivatives more selective and/or more potent than the natural compound. New exciting advances are expected soon and we can wait for them drinking tea.

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