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The potential therapeutic effects of ergothioneine in pre-eclampsia

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ABSTRACT

Ergothioneine (ERG), is a water-soluble amino acid that is derived entirely from dietary sources. It has received much attention as a therapeutic agent due to its anti-oxidant properties, and there are claims of preferential accumulation within high oxidative stress organs. Pre-eclampsia, a condition accompanied by increased oxidative stress, is one of the leading causes of maternal morbidity and mortality. Despite intense research efforts, its aetiologies remain somewhat unclear and there are still no effective treatment options. Clinical trials of the anti-oxidants vitamin C and vitamin E have proven largely ineffective with little improvement in clinical outcome or even a negative response. This could be explained in part by their inability to permeate the plasma and mitochondrial membranes and scavenge mitochondria-derived superoxide species, and for the former by the fact that it is actually a pro-oxidant in the presence of unliganded iron. ERG accumulates within tissues through the action of a specific organic cation transporter, SLC22A4 (previously referred to as OCTN1), which is possibly also expressed in mammalian mitochondria. Mitochondrial dysfunction has been implicated in a variety of vascular diseases including pre-eclampsia. This review discusses the use of ERG as a possibly mitochondrial-targeted anti-oxidant, focusing on its physical properties, potential mechanisms of action, safety profile and administration in relation to pregnancies complicated by pre-eclampsia.

1. Introduction

A disorder of late pregnancy, pre-eclampsia is the leading cause of maternal mortality accounting for 18% of maternal deaths worldwide (~77,000 deaths per year) [1]. Pre-eclampsia complicates 5% of nulliparous pregnancies and ~ 4 million women per annum [2]. The disease aetiology is thought to involve poor immunoregulation causing deficient trophoblast invasion and spiral artery remodelling leading to defective placentation [3,4]. Consequent, placental ischaemia leads to oxidative stress, with release of synctiotrophoblast debris into the maternal circulation provoking a systemic inflammatory immune response and release of plasma mediators: these include soluble fms-like tyrosine kinase-1 (sFLT), endoglin (sENG) and endothelin-1 (ET-1) [5–8]. Because the vascular endothelium relies on pro-angiogenic factors, the release of anti-angiogenic factors by the placenta into the maternal circulation is a potential cause of the endothelial dysfunction observed in pre-eclampsia.

Currently, other than delivery, there is no effective treatment for pre-eclampsia, with clinicians limited to prophylactic treatment with aspirin and increased surveillance. Numerous publications over the past two decades have supported the hypothesis that oxidative damage is involved in the pathophysiology of pre-eclampsia [9–19]. However, the results of clinical trials using classical small molecule anti-oxidants (vitamin C, vitamin E) have been largely disappointing, with little improvement in clinical outcome [20]. This possibly reflects these molecules' inability to penetrate to the central cellular source of reactive oxygen species – the mitochondria and its matrix. However not all reactive oxygen species are equally reactive/toxic (indeed peroxide and superoxide are even used as signalling molecules). In the case of ascorbate, it also probably reflects the fact that this is actually pro-oxidant and not anti-oxidant in the presence of unliganded iron, which can create the very damaging hydroxyl radicals via the Fenton reaction [21,22]. This review focuses on a potential new therapeutic agent for pre-eclampsia: L-Ergothioneine (ERG). ERG is a naturally occurring anti-oxidant discovered over a century ago in the rye ergot. Recent evidence from cellular and animal models have shown that cells lacking ERG are more susceptible to oxidative stress [23–27].

2. Ergothioneine

The unusual amino acid ergothioneine (also known as 2-mercaptohistidine trimethylbetaine; IUPAC name (2S)-3-(2-Thioxo-2,3-dihydro-1H-imidazol-4-yl)-2-(trimethylammonio)propanoate) (Fig. 1) was discovered by Charles Tanret in 1909 while investigating the ergot fungus,

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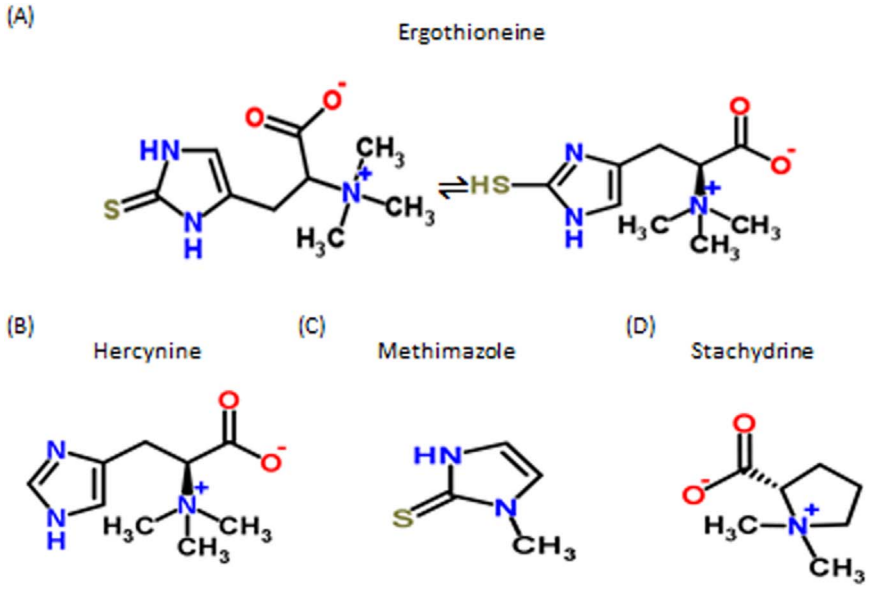

Fig. 1. Structure of thione-thiol tautomers of ergothioneine (2-mercaptohistidine trimethylbetaine) (A). In solution at physiological pH, ergothioneine exists predominantly in the thione rather than the thiol form, which ensures its resistance to autoxidation. Ergothioneine shares structural similiarities with (B) hercynine, (C) methimazole and (D) stachydrine (proline betaine).

Table 1
The concentration of L-Ergothioneine in body fluids.

	ERG (μmol/L ± SD)
Whole Blood	66 ± 2.2
Plasma	1.1 ± 0.3
Urine	0.2 ± 0.2
Saliva	0.6 ± 0.2

Data reproduced from Sotgia et al. [54].

Claviceps purpurea that devastated rye grains [28]. It is a dietary water-soluble amino acid, derived from histidine, which is synthesised mainly by non-yeast fungi (especially basidiomycetes), actinobacteria [24], methylotrophs [29] and cyanobacteria [30]. Numerous physiological roles of ERG have been proposed including cation chelation (Cu^{2+} in particular) [31,32], immune regulation, regulation of gene expression and most widely as a direct anti-oxidant due to its preferential concentration in high O_2 stress organs: liver, kidneys, erythrocytes, eye lens and seminal fluid [24,26,32–53]. Despite ERG's high concentration and ubiquitous presence, all mammalian ERG is derived from dietary sources with typical whole blood concentrations of 66 ± 2.2 μmol/L [54] (Table 1). To date, only one study has investigated the pharmacokinetics of ERG administration in human subjects [23]. In this study, healthy human subjects were administered either a 5 mg or 25 mg dose every morning for one week. ERG was rapidly absorbed and retained within the tissue/plasma with relatively low urinary excretion (< 4% of administered dose). Furthermore, a decrease in markers of oxidative stress was observed, but these changes did not reach significance. There is retrospective evidence to suggest patients with features of metabolic syndrome who consume at least 100 g of *Agaricus bisporus* (white button mushrooms, a major source of ERG) have increased antioxidant biomarkers compared to controls, with no change in lipid peroxidation markers [55]. The rapid uptake and retention of ERG in combination with the above data suggests that the amino acid has an important physiological function but perhaps only under conditions of oxidative stress.

Fig. 2 gives an overview of this article in the form of a 'mind map' [56].

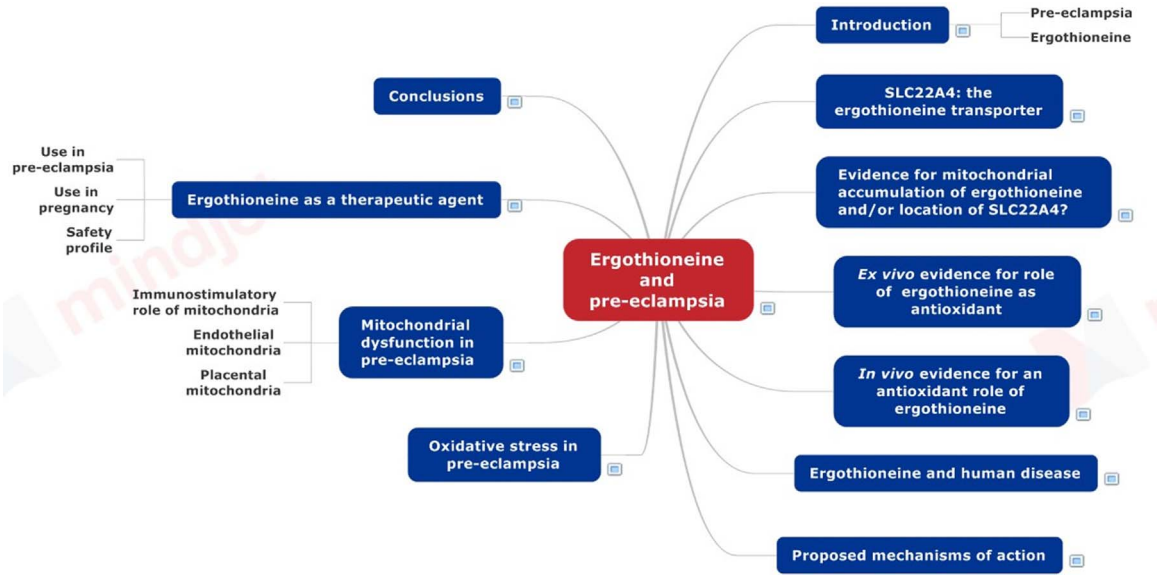

Fig. 2. A mind map of the article contents.