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Ectoine as a promising protective agent in humans and animals

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Ectoine is a compatible water molecule-binding solute (osmoprotectant) produced by several bacterial species in response to osmotic stress and unfavourable environmental conditions. This amino acid derivative can accumulate inside cells at high concentrations without interfering with natural processes and can protect the cell against radiation or osmotic stress. This brief review presents the current state of knowledge about the effects of ectoine on animals and focuses on its practical use for enzyme stabilisation, human skin protection, anti-inflammatory treatment, inhibitory effects in neurodegenerative diseases, and other therapeutic potential in human or veterinary medicine.

KEY WORDS: *cell protection; compatible solute; macromolecular stability; osmoprotectant*

Various organisms have developed different mechanisms to protect themselves against stress caused by environmental factors such as drought or extreme temperatures. Bacteria, especially those living in extreme environments, have the ability to produce compounds of small molecular weight known as compatible solutes or osmoprotectants, which do not interfere with cellular processes. They can accumulate to high concentrations and prevent cell dehydration (1). According to the structure, compatible solutes belong to the following groups: sugars (sucrose, trehalose), polyols (sorbitol, glycerol, mannitol, mannosyl-glyceramide, mannosyl-glycerol), *N*-acetylated diamino acids (*N*-acetylglutaminylglutamine amide), betaines (betaine, glycine, and deritatives), and amino acids and derivatives (proline, glutamate, glutamine, alanine, ectoine, and hydroxyectoine).

These substances strongly bind water molecules and stabilise macromolecules. Although their mechanism of action is not entirely known, there are several hypotheses explaining biophysical principles by which they act. The most widely accepted hypothesis is the "preferential exclusion model", according to which osmoprotectants do not interact directly with the macromolecule in an aqueous solution but are repelled to the bulk region, increasing macromolecule's hydration and thereby preventing its denaturation (2-4).

Ectoine (1,4,5,6-tetrahydro-2-methyl-4-pyrimidine carboxylic acid; for structure see Figure 1a) is a water-binding zwitterionic amino acid derivative (142,156 Da), first isolated from *Ectothiorhodospira halochloris* (5). It is also produced and accumulated by other, mainly aerobic, chemoheterotrophic and halophilic bacteria, such as alpha- and gammaproteobacteria and *Actinobacteridae*, in which it stabilises cell membranes, enzymes, and nucleic acids at extreme temperatures or higher salt concentrations (6). Ectoine synthesis from its precursor, L-aspartate-β-semialdehyde is catalysed by ectoine ABC enzymes, including diaminobutyric acid (DABA) acetyltransferase (ectA), DABA aminotransferase (ectB), and ectoine synthase (ectC) (7). Genes encoding these enzymes are organised in either ectABC or ectABC-ask operons (8).

A number of biophysical studies show that ectoine binds water molecules even better than some other osmoprotectants such as glycerol (9, 10) and that it is well tolerated by humans, animals, and various cell cultures. In fact, ectoine retains strong hydration properties even at high NaCl concentrations (11).

The aim of this brief review is to present the current state of knowledge about the effects of ectoine on animals and discuss its practical use in enzyme stabilisation, human skin protection, anti-inflammatory treatment, prevention of neurodegenerative diseases, and other therapeutic potentials in human or veterinary medicine.

Skin protection

Ectoine has widely been used in cosmetic anti-ageing and moisturising creams to improve skin resistance to surfactants in skin cleansing solutions (12). It is an effective long-term moisturiser that prevents dehydration of the epidermis, even superior to the well-known membrane

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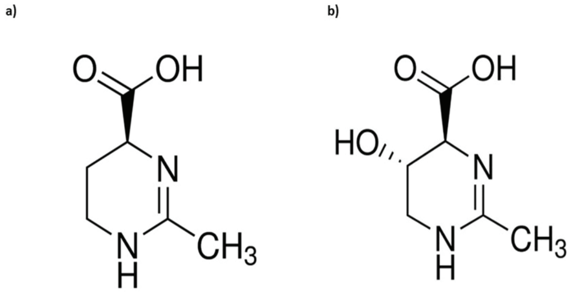

Figure 1 *Structural variants: ectoine (a) and hydroxyectoine (b)*

stabiliser phosphatidylcholine. Some authors suggest that at relatively low concentrations (up to 500 μmol L^{-1}) it can also be used as a whitening agent because of its inhibitory effect on melanin synthesis in B16-F0 and A2058 melanoma cell lines and on mushroom and cellular tyrosinase activities (13). Ectoine also alleviates skin inflammation and is currently recommended for the treatment of moderate atopic dermatitis (14).

In addition, ectoine strongly absorbs ultraviolet (UV) radiation and protects DNA from breaking down in various cell types (15; 16). Grether-Beck et al. (17) reported that ectoine reduced UV-A-induced ceramide signalling response in human keratinocytes, while Buenger et al. (16) reported protective effects against UV radiation in immunocytes and Langerhans cells.

Stabilising enzyme activity

A number of studies have indicated that ectoine increases the stability of enzymes maintaining hydration and thereby reducing protein susceptibility to denaturation. Interestingly, this amino acid derivative does not interact directly with protein surfaces but rather it forms a molecular net holding water molecules close to the macromolecule (10, 18, 19). Moreover, Roychoudhury et al. (20) have shown that ectoine, like other compatible solutes, strengthens intramolecular interactions essential for protein stability. Ectoine reduces denaturation of enzymes induced by a rapid change of temperature. It prolongs the activity of lactate dehydrogenase (LDH) and phosphofructokinase, enzymes that are normally sensitive to freeze-thawing, heating, and freeze-drying (21). It also increases the stability of phytase, ribonuclease-A, and polymerase of the double-stranded DNA at elevated temperature (22, 23).

Tenne et al. (24) found that ectoine derivative hydroxyectoine (for structure see Figure 1b) is even superior to ectoine in protecting against elevated temperatures.

Ectoine has also been reported to protect macromolecules against proteolytic agents. For example, zymogens chymotrypsinogen and trypsinogen were resistant to proteolysis by enteropeptidases (25). Another study showed that antibodies treated with ectoine were less susceptible to proteolytic degradation by pepsin (26).

In addition, ectoine can inhibit HIV replication (23) and can also stabilise retroviral vectors for gene therapy, which may be a useful property, because these vectors usually lose their infectivity during long-term storage and transport (27).

Cell protection

Various environmental stressors such as heat or toxic chemicals may impair the cell membrane function and result in cell dehydration and denaturation. Harishchandra et al. (28) propose that ectoine increases cell membrane fluidity to cope with extreme conditions such as high temperature or osmotic pressure. A recent biophysical study by Zacchai et al. (10) showed that ectoine is excluded from the hydration layer at the membrane surface and does not affect membrane molecular dynamics. Moreover, improved hydration of the cell surface thanks to ectoine increases intermolecular spacing and boosts the mobility of the lipid head groups in the cell membrane (Figure 2) (29).

Different types of cells subjected to high temperature tend to produce chaperone proteins such as heat shock proteins (Hsp), which repair misfolded peptides. Ectoine seems to affect their synthesis and is speculated to act as a chaperone molecule itself (30). Buommino et al. (31) reported that heat-stressed keratinocytes incubated with ectoine had higher levels of Hsp70 and inhibited the production of pro-inflammatory signals.

Some studies indicate that ectoine shows promising properties against the detrimental effects of some toxic compounds. In a study by Graf et al. (12) ectoine-treated human erythrocytes were more resistant to membrane-damaging sodium dodecyl sulphate detergent than untreated cells. Our recent study (32) has shown that ectoine has a potential to block pore-forming toxins, as the isolated bovine erythrocytes treated with ectoine turned out to be less sensitive to staphylococcal alpha-haemolysin. Interestingly, the toxin monomers preincubated with ectoine were less cytotoxic than those added to the cell suspension simultaneously with ectoine, which suggests that ectoine blocks the unfolding of the toxin monomers and thus prevents the formation of transmembrane pores in the cell membrane. These findings suggest that ectoine may be useful in protecting erythrocytes from staphylococcal haemolysins. Little is known, however, about ectoine protective effects against toxins produced by other bacterial species, mycotoxins, and toxic proteins found in animal venom. Future research should answer whether the osmoprotectant could be an effective antidote.

Alleviation of inflammatory reaction

Ectoine effectively alleviates inflammation, such as the experimentally induced colitis in rats (33) or nanoparticle-induced neutrophilic lung inflammation (34). It can also mitigate inflammatory reactions in the lung epithelial cells after inhalation of carbonaceous nanoparticles in mice. However, this effect was not observed when lung inflammation was induced by bacterial lipopolysaccharide (35). Peuschel et al. (36) reported that inhalational exposure

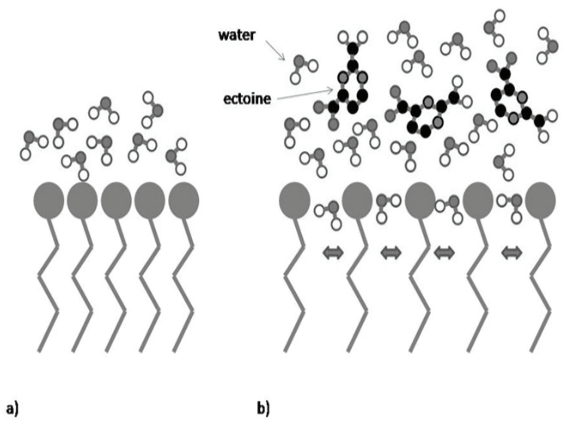

Figure 2 *Influence of water molecules alone (a) and aqueous solution of ectoine (b) on lipid monolayer. Ectoine increases the distance between lipid molecules and improves membrane fluidity.*

to carbon nanoparticles in mice resulted in the accumulation of ceramides in lipid rafts of cell membranes, activation of epidermal growth factor receptor (EGFR), and lung inflammation. Animals additionally treated with ectoine, however, showed milder allergic reactions because ectoine seems to have inhibited ceramide-mediated EGFR phosphorylation. Another study showed that ectoine and hydroxyectoine enhance lung surfactants, which suggests their potential use as supporting factors in inhalation therapy (37).

Ectoine was also found to protect ileal mucosa against ischaemia and reperfusion injury, which are common complications after the small bowel transplantation (38, 39). Alleviating the inflammatory reaction is related to the improvement of intestinal barrier and reduction of cytokine production (33).

Nasal spray and air drops containing ectoine are the new approaches to treating allergic rhinitis, rhinoconjunctivitis, and dry eye syndrome (29). Some studies showed that products containing ectoine may be a better alternative to other products, as they reduce ocular and nasal symptoms with no side effects (40-42). Promising effects such as reduction of nasal airway obstruction and crust formation were also observed in patients with rhinitis sicca anterior treated with nasal spray containing ectoine alone or in combination with dexpanthenol (43). Moreover, a recent study has shown that a mouth and throat spray containing ectoine can be very effective in the treatment of acute pharyngitis and laryngitis (44).

Cryoprotection

Compatible solutes such as ectoine and hydroxyectoine are effective agents in cryopreservation. Bissoyi and Pramanik (45) reported it to be an efficient additive in cryoprotective media for mononuclear cells isolated from human umbilical cord blood. Their 10 % foetal bovine serum medium containing a combination of hydroxyl ethyl starch, ectoine, and co-enzyme Q10 yielded the highest, 93 % viability of mononuclear cells. Sun et al. (46) reported that both ectoine and hydroxyectoine protected human endothelial cell line HPMEC-ST1.6R or mesenchymal stem cells and suggested that they may be used in cryobiology as an alternative to the toxic dimethyl sulphoxide (DMSO). One study on rats (47) showed that adding hydroxyectoine to the histidine-tryptophan-ketoglutarate solution reduces the cold ischaemic preservation injury of livers donated after cardiac death and used for transplantation. Ectoine was also successfully used as a cryoprotectant of human erythrocytes, as it prevented slow-freezing cell damage (48).

Protection against neurodegenerative diseases

Some pathological processes like amyloid formation and aggregation induce neurodegenerative diseases. Ectoine was found to prevent amyloid formation and delay the onset and progression of Alzheimer's disease (49). Other studies have shown that this amino acid derivative inhibits insulin amyloid formation and interacts with prion aggregation responsible for transmissible spongiform encephalopathies (50-52).

Protection of invertebrates against environmental stressors

Little is known about how ectoine acts in invertebrates. In our earlier studies (53-55) ectoine showed protective effects in *Daphnia magna* subjected to high temperature by inhibiting heat shock protein Hsp70, catalase activity, and NO radicals. Moreover, ectoine-treated *Daphnia magna* were more resistant to toxic disinfectants formaldehyde and hydrogen peroxide than untreated controls, as manifested through significantly lower mortality rates, better swimming activity, and better physiological parameters such as heart rate and thoracic limb activity (56). In practice, it could be used as a stabilising agent during the transport of some edible species sensitive to different forms of stress.

CONCLUSION

As ectoine is a potent protective agent against different forms of stress without toxic side effects, its current use in biotechnology, cosmetics, and medicine, leaves a lot of room for many innovative applications. However, since the reviewed literature covers a wide range of studies of different complexity, from isolated macromolecules and cell cultures to various animal species, the protective effects of ectoine observed in simple systems may fail in more complex ones. Moreover, ectoine inactivates some molecules; therefore its use may be limited due to possible interactions with other pharmaceuticals.

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Obećavajuća zaštitna svojstva ektoina u ljudi i životinja

Ektoin je kompatibilni osmolit (osmoprotektant) koji proizvodi više bakterijskih vrsta kao odgovor na osmotski stres i nepovoljne uvjete u okolišu. Ovaj se derivat aminokiseline može nakupiti i dosegnuti visoke razine u samoj stanici a da pritom ne ometa prirodne stanične procese. Usto štiti stanicu od zračenja ili osmotskoga stresa. Svrha je ovoga članka dati kratak pregled dosadašnjih spoznaja o djelovanju ektoina u životinja, s posebnim osvrtom na praktičnu primjenu ovoga osmoprotektanta u stabilizaciji enzima, zaštiti kože u ljudi, protuupalnoga liječenja, sprječavanja ili usporavanja neurodegenerativnih bolesti te u ostalim oblicima liječenja ljudi i životinja.

KLJUČNE RIJEČI: *kompatibilni osmolit; osmoprotektant; stabilnost makromolekula; zaštita stanica*