Current Trends in Microbiology
Vol. 15, 2021

Short Communication

N-chlorotaurine: Random biochemical drug or evolution-tailored masterpiece?

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ABSTRACT

N-chlorotaurine (NCT), a product of activated human granulocytes and monocytes, belongs to the long-lived oxidants of innate immunity. It is involved in the inactivation of invading pathogens because of its microbicidal properties and in termination of inflammation because of its anti-inflammatory properties. The synthetically manufactured sodium salt of NCT enables the introduction of NCT as an endogenous anti-infective and antiseptic in medicine for topical treatment of infections in different body regions. Compared to highly reactive oxidants, the low reactive NCT has the advantages of better tolerability and applicability of higher concentrations. Moreover, in body fluids and exudates, not only lower consumption of oxidation capacity, but also desirable enhancement of microbicidal activity because of transchlorination reactions, occur. All these properties in combination, originating from evolution, render NCT a masterpiece useful in infectiology.

KEYWORDS: N-chlorotaurine, chloramines, antiseptic, hypochlorous acid, anti-infective, infection, innate immunity.

ABBREVIATIONS

NCT – N-chlorotaurine

INTRODUCTION

In a preceding paper entitled "Less is more, transferring a principle from art to science", the novel biological oxidant N-chlorotaurine (NCT) was introduced as an efficient antiseptic with high tolerability caused by a medium oxidizing potency which significantly differs from that of the strong oxidant hypochlorous acid, HOCl [1]. In other words, NCT kills invading virulent pathogens without damaging adjacent living tissue. This has been confirmed by clinical efficacy in controlled trials in conjunctivitis, crural ulcerations, external otitis, and dental plaque and in smaller trials and cases in other body regions such as the urinary bladder (for review see [2, 3]).

Beyond all doubt, the concept of 'sufficient microbicidal activity coupled with high tolerability' is an important one. In the present report, we provide a comprehensive explanation for these welcome and surprising properties based on structural conditions and mechanisms of action.

Oxidative power depends on structural conditions

Deliberating on the basic principles that control the mechanism of disinfection *in vivo* might provoke the question "Upon what rests the uniqueness of the oxidizing agent N-chlorotaurine?". A possible answer is the following: Based on previous studies and case applications, NCT turned out to be an effective anti-infective upon topical application to different body regions [2, 3]. Even inhalation is well tolerated and renders the substance promising for treatment of patients suffering from the present pandemic Covid-19 [4, 5]. Tracing back the background of research and scrutinizing the disinfecting activity of oxidants, hypochlorous acid (HOCl) indeed revealed an excellent disinfecting

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potency, which, however, was accompanied by an unwanted strong irritation of adjacent tissue [6, 7]. The next step was finding that the reaction product of taurine and hypochlorous acid, which is the natural oxidant NCT,

$H_2N\text{-}CH_2CH_2\text{-}SO_3H + HOCl \rightarrow Cl\text{-}HN\text{-}CH_2CH_2\text{-}SO_3^- + H_2O$

represents the ideal reagent which destroys virtually all kinds of pathogens, moreover, without noteworthy irritation [2]. This justifies by all means to specify NCT as a comparatively mild, but effective natural oxidant.

The fact that NCT is a mild oxidant can be explained by Pauling's electronegativity principle, which teaches that the positive partial charge of the chlorine atom in the O-Cl bond (χ = 3.44 - 3.16 = +0.28) clearly excels the one in the N-Cl bond (χ = 3.04 – 3.16 = -0.12) [8]. To the latter, therefore, a lower oxidizing potency can be assigned. This, too, explains the qualification of NCT and other N-Cl compounds as comparatively mild oxidants. In other words, the transhalogenation from HOCl to taurine is characterized by the transfer of the whole oxidation capacity to the taurine molecule [7]. Since this includes the conversion of an O-Cl bond into an N-Cl bond, the oxidizing activity is reduced as clarified above.

Stability depends on structural conditions

Discussing the specifications of NCT, scientific reliability requires to reveal NCT's somewhat reduced stability, initiated by separation of HCl and the subsequent hydrolysis of the intermediary imine, which delivers sulfoacetaldehyde [9].

$ClHNCH_2CH_2SO_3^- \rightarrow HN{=}CHCH_2SO_3^- + HCl$

$HN{=}CHCH_2SO_3^- + H_2O \rightarrow O{=}CHCH_2SO_3^- + NH_3$

In spite of these facts, which classify the N-Cl bond as the key specification for a mild oxidant, it has to be recorded that attempts to manufacture derivatives of NCT were successful, yielding compounds (e.g. the dimethylated derivative of NCT) which indeed were more stable than NCT [10, 11]. This property could be attained, e. g., by introducing two methyl groups to substitute both of the hydrogens at the ß-carbon of NCT, which rules out the separation of HCl in $ClHNC(CH_3)_2CH_2SO_3Na$ and the following transformations to an imine and subsequently to sulfoacetaldehyde. This type of decay is typical for all organic chloramines bearing C-H functions adjacent to the nitrogen. In case of NCT, it can be suppressed by storage of the crystalline sodium salt at freezing temperatures. A decrease of the oxidation capacity of < 10% can be warranted for 4 years at minus 20 °C and for > 10 years at minus 80 °C. By this, the lack of complete stability of NCT can be overcome.

An optimal compromise between efficacy and tolerability depends on structural conditions

At this point an astonishing historical account, published as early as 1831, should be cited, which contains the proposal to cure pulmonary tuberculous consumption by inhalation of iodine vapours and even chlorine gas [12, 13]. Because of absence of sufficient tissue penetration and doubtful efficacy, however, this method was not pursued further. During World War 1, hypochlorous acid and chloramine T (N-chloro-p-toluenesulfonamide) were applied for treatment of wound infections [6, 14]. At that time, chlorine consumption and irritative effects depending on the oxidative activity were already documented [6, 14]. Because of such adverse effects and impossibility of systemic application due to immediate reduction of the oxidation capacity by blood components, these substances were largely replaced by antibiotics in the next decades. With upcoming resistance problems with antibiotics and the finding of the natural long-lived oxidants, chloramines with low reactivity produced from the reaction of HOCl with amino compounds *in vivo* [15, 16], the situation started to change again. Particularly NCT as the most abundant natural long-lived oxidant [17], which can be synthesized chemically, too, gained interest [2]. Its mild activity allows clinical application of high concentrations (mainly around 1%, 55 mM) without toxic or systemic adverse effects and almost without local irritative effects [2, 3]. While highly reactive oxidants like HOCl are consumed much more by reaction with organic material and while they lose microbicidal activity in this environment, NCT maintains the majority of its oxidative capacity, and, moreover, its microbicidal activity is enhanced [1, 18, 19]. The latter is caused by reaction with ammonium chloride (NH_4Cl) and transchlorination in equilibrium

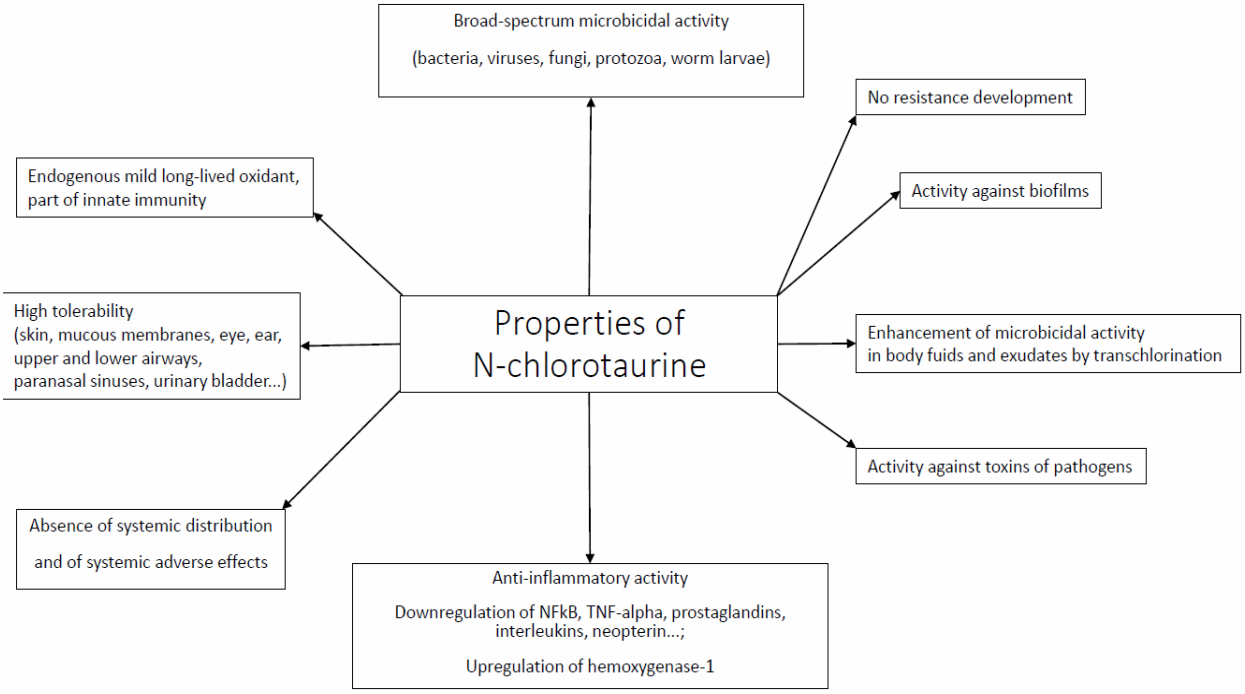

Fig. 1. Survey on the properties of NCT.

to monochloramine (NH_2Cl), which is more lipophilic and penetrates pathogens better [2].

$ClHNCH_2CH_2SO_3^- + NH_4Cl$ <------>
$H_2NCH_2CH_2SO_3^- + NH_2Cl + H^+ + Cl^-$

Considering these facts, the high abundance of NCT in activated human granulocytes and monocytes obviously derived from evolution, makes a lot of sense. At first, taurine detoxifies HOCl upon formation of NCT. Second, NCT maintains microbicidal activity over a longer time than highly reactive oxidants. Third, because of its anti-inflammatory activities, it is thought to be involved in termination of inflammation [7, 20]. Using 1000-fold higher pharmacological concentrations of NCT (55 mM versus the 50 µM natural one), enhances the microbicidal activity and maintains outstanding tolerability [2]. Small changes of the molecule, such as manufacturing of dimethylated derivatives [10, 11], obviously impaired the optimal compromise of efficacy and tolerability of NCT. Therefore, the natural compound remains the most favorable till date due to the combination of its properties (Fig. 1). Even inhalation of NCT in high concentration (1%) is very well tolerated and for the first time allows the application of an antiseptic in sufficient amounts also to the lower airways [4], which, among others, renders it a promising medication for the present pandemic [5, 21, 22].

CONCLUSION

Summarising the hitherto established evidence emphasizes NCT as an agent bearing the unique feature as the – currently - sole chemical representative being capable to fulfil the mentioned tasks with excellent performance and utmost subtlety. This, moreover, unequivocally answers the question implied in the title of this paper. NCT is a masterpiece of evolution.

ACKNOWLEDGEMENTS

We are grateful to Andrea Windisch for her excellent technical assistance in the studies on NCT.

FUNDING

There was no separate funding for this publication.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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