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Lipoic Acid in the Treatment of Smell Dysfunction Following Viral Infection of the Upper Respiratory Tract

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Objectives/Hypothesis: **The study aimed to investigate the potential therapeutic effects of α-lipoic acid in olfactory loss following infections of the upper respiratory tract. Possible mechanisms of actions include the release of nerve growth factor and antioxidative effects, both of which may be helpful in the regeneration of olfactory receptor neurons.** ***Study Design:*** **Unblinded, prospective clinical trial.** ***Methods:*** **A total of 23 patients participated (13 women, 10 men; mean age 57 y, age range 22–79 y; mean duration of olfactory loss, 14 mo; range, 4 to 33 mo); 19 of them were hyposmic and 4 had functional anosmia. Alpha-lipoic acid was used orally at a dose of 600 mg/day; it was prescribed for an average period of 4.5 months. Olfactory function was assessed using olfactory tests for phenyl ethyl alcohol odor threshold, odor discrimination, and odor identification.** ***Results:*** **Seven patients (30%) showed no change in olfactory function. Two patients (9%) exhibited a moderate decrease in olfactory function; in contrast, six patients (26%) showed moderate and eight patients (35%) remarkable increase in olfactory function. Two of the 4 patients with functional anosmia reached hyposmia; 5 of 19 hyposmic patients became normosmic. Overall, this resulted in a significant improvement in olfactory function following treatment (*P* = .002). At the end of treatment parosmias were less frequent (22%) than at the beginning of therapy (48%). Interestingly, recovery of olfactory function appeared to be more pronounced in younger patients than in patients above the age of 60 years (*P* = .018).** ***Conclusions:*** **The results indicate that α-lipoic acid may be helpful in patients with olfactory loss after upper respiratory tract infection. However, to judge the true potential of this treatment, the outcome of double-blind, placebo-controlled studies in large groups of patients must be awaited, especially when considering the relatively high rate of spontaneous recovery in olfactory loss after upper respiratory tract infection.** ***Key Words:*** **Olfaction, regeneration, therapy.**
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INTRODUCTION

Viral infections of the upper respiratory tract are among the most frequent causes associated with smell disorders.[1–3] Although the pathogenesis of postviral olfactory dysfunction is unknown, histological studies have shown the destruction of the olfactory epithelium with an irregular arrangement of the mucosal layers including loss of olfactory receptor cells indicating the involvement of the peripheral olfactory system.[4,5] Hence, postviral smell dysfunction seems to be due to an impairment of the olfactory neurons, both in function and in numbers. Although numerous treatments have been tried in postviral anosmia (e.g., corticosteroids, zinc, vitamin A), no pharmacological therapy has been established to date.[2,6–8] This difficult situation is underlined by the fact that, when "parosmia"/"troposmia" (distorted olfactory sensations elicited through odors) is present,[9,10] in some patients surgical removal of the olfactory epithelium may be considered as a cure.[11]

When searching for potential candidates for the pharmacological treatment of olfactory dysfunction we came across α-lipoic acid (aLA), which is used in the treatment of diabetic neuropathy.[12–15] The effect of aLA is well described both in experimental animals and in humans (for review see Packer et al.[16]). It is known to stimulate the expression of nerve growth factor, substance P, and neuropeptide Y.[17–19] It enhances motor nerve conduction velocity as well as microcirculation.[20,21] Further, because of its potent antioxidative effects, aLA also has neuroprotective capabilities indicating that aLA is suited to treat neural damage involving free radicals.[22]

Alpha-lipoic acid is a fatty acid that penetrates the blood–brain barrier. It is taken up into cells where it is metabolized to its active metabolite, dihydro-lipoic acid (dLA), which is also released into the extracellular space.[16] Singlet oxygen, peroxynitrite, hypochlorous acid, and hydroxyl radicals are reduced by aLA.[16] Its active metabolite also leads to a decrease in superoxide and peroxyl radicals.[23] Dihydro-lipoic acid regenerates vita-

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min E by elevating intracellular glutathione concentrations, and it restores thioredoxin and vitamin C.[21,23,24] Thus, both aLA and dLA appear to be useful in the repair of oxidative lesions. Based on this information, aLA was thought to be a good candidate for the treatment of post–upper respiratory tract infection (post-UTRI) dysfunction.

Alpha-lipoic acid is approved for the treatment of neuropathy in diabetes mellitus and is safe. Intoxications following administration of aLA only are not observed; no severe side effects have been reported following oral administration. However, before initiation of a large scale, double-blinded study, aLA should be tried in an open, unblinded pilot study to determine whether it has promising effects that would justify an extensive follow-up.

PATIENTS AND METHODS

A total of 23 patients participated (13 women, 10 men; mean age, 57 y; age range, 22–79 y; mean duration of olfactory loss, 14 mo; range, 4–33 mo); 19 of them were hyposmic and 4 had functional anosmia.[25] Patients presented at our smell and taste clinic (at the Department of Otorhinolaryngology, University of Dresden Medical School, Dresden, Germany) with complaints of olfactory dysfunction following a viral infection of the upper respiratory tract; the duration of their condition ranged from 4 to 33 months. The diagnosis "post-URTI olfactory dysfunction" was based on the patient's history and a thorough clinical examination by an otorhinolaryngology specialist. Post-URTI olfactory dysfunction was stated as a diagnosis when the patient reported typical symptoms of a common cold just before the onset of the olfactory loss without an interval between the infection and the smell dysfunction. Patients with neurodegenerative disorders were excluded from the study. Other potential causes of smell loss,[26] including head trauma, inflammatory affections of the nasal cavity (e.g., polyps or allergic reactions), nasal tumors, or brain tumors, had been excluded. The study was approved by the local ethics committee (EK56042001); it was conducted according to the guidelines on biomedical research involving human subjects (Declaration of Helsinki).

Alpha-lipoic acid was used at a dose of 600 mg/day; patients took aLA for 3 to 11 months (median period, 4 mo). Olfactory function was assessed before and at the end of the treatment period using olfactory tests for phenyl ethyl alcohol odor threshold, odor discrimination, and odor identification. Specific, standardized questions were asked in relation to the presence of parosmia.

Olfactory Testing

For assessment of olfactory function, pen-like odor-dispensing devices ("Sniffin' Sticks") were employed.[25,27] Testing included three tests of olfactory function, namely, tests for phenyl ethyl alcohol odor threshold, odor discrimination, and odor identification. For odor identification, 16 odorants were presented to each subject, who was free to sample the odors as often as necessary to identify the odors from a list of four descriptors. The experimenter presented odor pens separated by an interval of at least 30 seconds to prevent olfactory desensitization. Odor discrimination was performed using 16 triplets of odorants. Subjects were presented with three odorants; the subject's task was to identify the sample that smelled different. Subjects were blindfolded to prevent visual detection of the target odor pens. They were allowed to sample each odor only once. Presentation of odor triplets was separated by at least 30 seconds. The interval between presentation of individual odor pens was approximately 3 seconds. Odor thresholds were determined using phenyl ethyl alcohol as the odorant; dilutions were presented in a geometric series. Presentation of the odorants was similar to that described above for the discrimination task. Again, subjects were blindfolded to prevent visual identification of the odor-containing pens. Three pens were presented to each subject in a random order; one pen contained the odorant at a certain dilution, and the other two pens, solvent only. The subject's task was to find out which of the three pens smelled different. Presentation of triplets occurred every 20 seconds, until subjects had correctly discerned the odorant in two successive trials, which triggered a reversal of the staircase. From a total of seven reversals the mean of the last four staircase reversal points was used as threshold estimate.[28] Results of the three individual olfactory tests were summed to a "threshold, discrimination, and identification (TDI) score," which is clinically used to estimate olfactory function.[25,27,29,30] Based on investigations in more than 1000 subjects, this TDI score also allows the classification into functional anosmia, hyposmia, and normosmia.[25] Olfactory sensitivity was classified as unchanged when the change in this TDI score was $\leq \pm 1.5$ points; a change of 5.5 points was used to separate moderate from remarkable changes of olfactory function.

Statistical Analysis

For statistical analysis, SPSS (Statistical Package for the Social Sciences, version 10.0, SPSS Inc., Chicago, IL) was used. Comparisons between measures obtained before and after treatment were performed using a t test for paired samples. Correlation analyses were performed according to Pearson. The α-level was set at 0.05.

RESULTS

Treatment with aLA was tolerated well by all subjects; no major side effects were reported. There were no dropouts. Patients with hyposmia or anosmia showed significant improvement in olfactory function following treatment as indicated by the change in the TDI score (t test, $t = 3.52$ [$P = .002$]) (Fig. 1 and Table I). With regard to the three individual tests, this was significant for odor discrimination ($t = 3.09$ [$P = .005$]); although odor thresholds and odor identification improved after therapy, these change missed statistical significance ($t = 1.76$ [$P = .093$] and $t = 1.05$ [$P = .31$], respectively).

Seven patients (30%) showed no change in olfactory function. Two patients (9%) exhibited a moderate decrease in olfactory function; in contrast, six patients (26%) showed moderate and eight patients (35%) remarkable increase in olfactory function. Two of the 4 patients with functional anosmia reached hyposmia; 5 of the 19 hyposmic patients became normosmic.[25] At the end of treatment, distorted olfactory sensations elicited through odors ("parosmia"/"troposmia"[9,10]) were reported by a smaller percentage of patients (22%) compared with the beginning of therapy (48%).

Recovery of olfactory function appeared to be more pronounced ($t = 2.56$ [$P = .018$]) in younger patients than in patients above the age of 60 years (the age of 60 y was the median age of the entire group). In addition, after data from one outlier had been left out, a weak but significant correlation was found between age and the change in the TDI score following treatment with aLA ($r_{22} = -0.52$ [$P = .013$]) (Fig. 2). In terms of improvement of olfactory function, no differences were seen between patients with a relatively short duration of olfactory dysfunction (<14 mo) and patients with a relatively longer duration of the olfac-

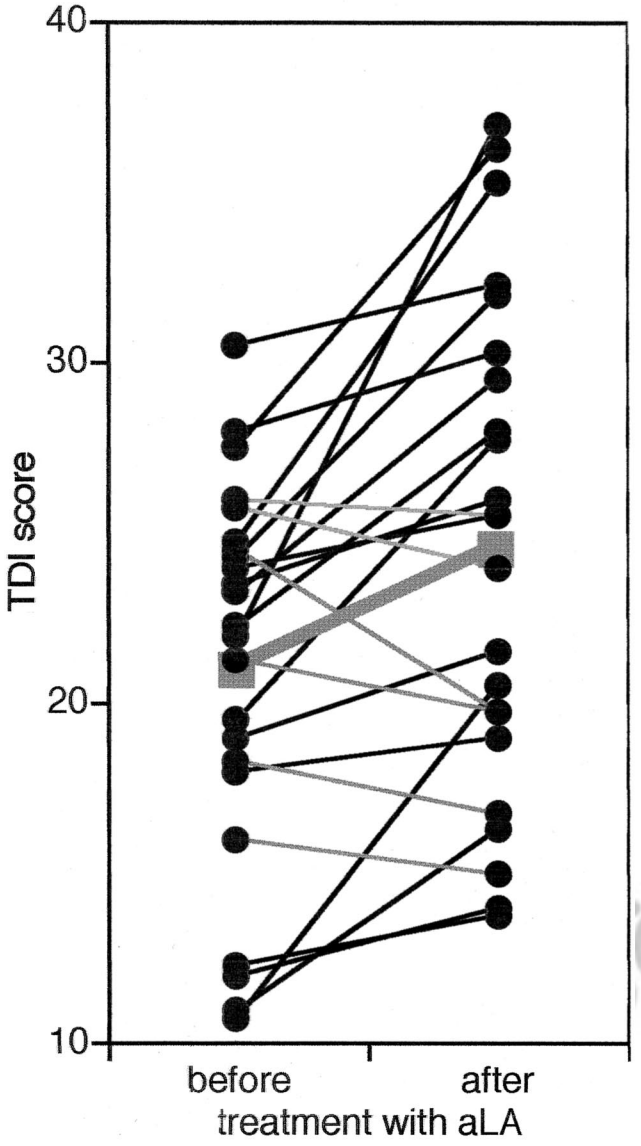

Fig. 1. Olfactory function expressed as "threshold, discrimination, and identification (TDI) score" before and after treatment with α-lipoic acid. Results for individual subjects are marked with filled black circles; mean values for the 23 patients are indicated by filled gray squares.

tory loss ($\geq$14 mo [14 mo was the median duration of olfactory loss]) (TDI score, $t = 0.65$ [$P = .52$]).

DISCUSSION

The present results indicate that aLA may be helpful in the treatment of post-URTI olfactory dysfunction; specifically, 1) olfactory sensitivity as measured by means of the TDI score significantly improved and 2) the rate of "parosmia"/"troposmia" decreased from 48% to 22%. Interestingly, during the mean observation period of 4.5 months, recovery of olfactory function appeared to be more pronounced in younger than in older subjects.

Our results encourage the conduct of double-blind, placebo-controlled studies in large groups of patients. These studies are necessary to judge the therapeutic potential of aLA in post-URTI olfactory dysfunction, especially when considering the relatively high rate of spontaneous recovery in post-URTI olfactory loss. This recovery is based on regeneration of olfactory receptor neurons from basal cells in the olfactory epithelium.[31,32]

TABLE I.
Descriptive Statistics of Results Obtained for Odor Thresholds, Odor Discrimination, and Odor Identification (means, standard errors; n = 23; in units—see text for details) Before and After Therapy With aLA.

	Before Treatment		After Treatment	
	Mean	SEM	Mean	SEM
Odor threshold	4.66	0.71	6.06	0.76
Odor discrimination	8.56	0.60	10.26	0.50
Odor identification	7.83	0.47	8.26	0.55

aLA = α-lipoic acid; SEM = standard error of mean.

Regeneration of olfactory function is a characteristic of post-URTI olfactory loss. In a summary of the literature up to the year 1988, Hendriks[1] reported that complete recovery of the sense of smell has been seen in 9 of 26 untreated patients (35%); he also presented data showing that 19 of 55 patients (35%) exhibited such recovery who had been reported in various clinical trials as receiving various treatments (e.g., strychnine, corticosteroids, or vitamin B). Summarizing results from nine different studies conducted between 1870 and 1977, Hendriks[1] found that recovery would occur in approximately 90% of the

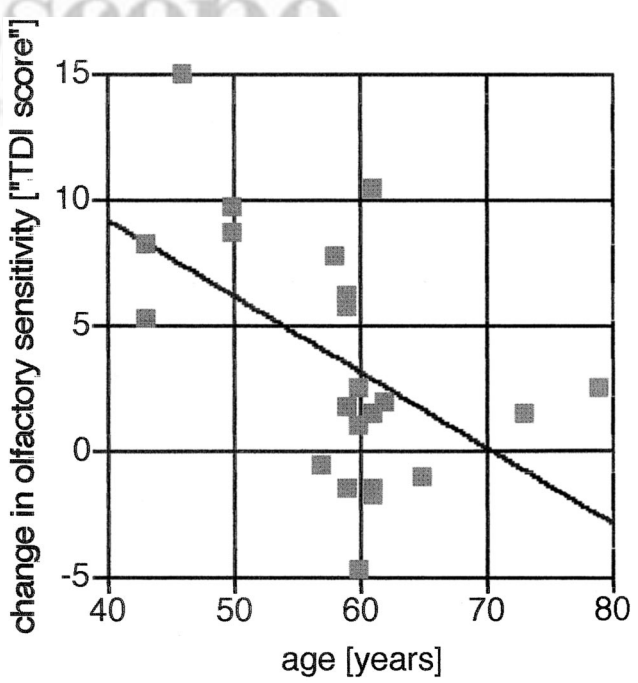

Fig. 2. Relation between age and change of olfactory function after therapy with α-lipoic acid (expressed as "threshold, discrimination, and identification [TDI] score"). Data from one outlier are not shown (age, 22 y; change of TDI score, 2.25). The line emphasizes the relation between age and change of olfactory function ($f(x) = -0.30^{*}\times + 21.3$) indicating that improvement is less likely in older patients.

subjects 12 months after the viral infection. More recently, similar changes have been reported. For example, after a period of 3 years, 19 of 21 patients scored higher in an odor identification test[33]; 13 of these 21 patients also reported an improvement in their sense of smell. In addition, following post-URTI olfactory loss, recovery has been reported by many other authors.[34,35] Further, using various treatments including systemic administration of vitamin B and adenosine triphosphate, Yamagishi et al.[5] reported that 22% of 70 patients with post-URTI olfactory loss exhibited full recovery, and an additional 20% of these patients reported moderate improvement.

Comparison of the previous results on post-URTI olfactory dysfunction with the present data must to be performed carefully, especially when considering that different methods and criteria were used to asses olfactory function and to judge the outcome of these tests. In any case, although the present study has provided promising results, the rate of spontaneous recovery asks for double-blind, randomized studies in a larger study group, and such an investigation is currently under way.

The present data supported the hypothesis that recovery of olfactory function is better in younger subjects. Subjects younger than 60 years of age exhibited significantly greater improvement in olfactory function than older subjects. The younger the subjects were, the better the degree of improvement was. This observation may relate to an age-related decreased (but still ongoing) proliferation of neurons in the olfactory epithelium, which has been shown in experimental rats.[36] In this scenario, it is thought that the production of new neurons does not keep up with loss. Other age-related factors potentially affecting olfaction include greater sensitivity to the effects of inflammation and reduced adrenergic innervation of the vasculature.[37] However, such an effect of age on olfactory recovery was not observed by Mori et al.[35] Using the T&T olfactometer (an odor threshold test with various odorants[38]), they investigated a large group of 244 subjects and did not find such a relationship. Although this discrepancy may be explained by differences in olfactory testing, further studies are needed to clarify this.

The present data do not support the idea that improvement of olfactory function would be better in patients in whom the viral infection occurred more or less recently. Observing this fact from a different angle, it argues for a steady improvement in olfactory function, regardless of whether olfactory loss had occurred 1 or 2 years ago. This interpretation emphasizes observations made by Duncan and Seiden,[33] who reported an increase in olfactory function even years after the incident that had caused olfactory loss (compare with Mori et al.[39]).

The present findings also indicated a reduction of "parosmia"/"troposmia" following treatment with aLA. Although their origin is unclear, these parosmias may result from the loss of functioning olfactory neurons, which would translate into the inability to form a complete "picture" of a given odorant.[10] According to Leopold,[40] peripheral causes of parosmias are suggested by the finding that most individuals with distortions have an intensity loss along with the distortion. In addition, he maintained that ". . .distortions seem to occur either during neuron death or regeneration. . .." This would indicate that the presently observed disappearance of such distortions would be another indicator of improved olfactory sensitivity.

CONCLUSION

Taken together, the present results indicate that aLA may be helpful in patients with post-URTI olfactory loss, which could fill a therapeutic void. However, to judge the true potential of this therapeutic approach, the outcome of double-blind, placebo-controlled studies in large groups of patients must be awaited, especially when considering the relatively high rate of spontaneous recovery in post-URTI olfactory loss.

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