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ANSWERING THE ACUTE QUESTION: HOW TO USE AMINOXYL (NITROXIDE) FREE RADICALS APPROPRIATELY TO REGULATE OXIDATIVE/NITROSATIVE STRESS AND AS POTENTIAL MEDICINES

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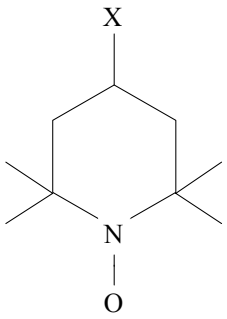
Abstract

Critical review of state-of-art pharmacological applications of aminoxyl (nitroxide) stable free radicals to avoid cytotoxic effects under oxidative and nitrosative stress is presented. A common feature of both types of paramagnetic species – nitric oxide (NO) and free nitroxide (aminoxyl) radicals – is a N–O moiety. A nitric oxide moiety, when placed into a saturated organic structure, looses its signaling function, demonstrates a unique triplet ESR spectrum, expresses the ability to interact with superoxide and NO toxic metabolic products as well, and preserves the number of biological activities. This might find an importance for future aminoxyl radicals' applications in pharmacology as anticancer, radioprotective, or antihypertensive drugs. Aminoxyl radicals are considered to be potent complementary medicines for combined use with nitric oxide inducers to avoid cytotoxic effects. To use aminoxyl free radicals as medicines, additional studies of their neurotropic effects are required.

Key words: nitric oxide, aminoxyl (nitroxide) free radicals, cardiovascular system, nitric oxide signaling, nitric oxide cytotoxic metabolites, nitroxide bioactivity, super oxide dismutase mimic activity.

The highly reactive and bioactive species of nitric oxide (NO) is well-known as an intra- and extracellular signaling messenger and neuromediator [1]. NO, being a messenger molecule and leading to vaso-relaxation, also represents an inorganic free radical, which is the only known free radical effector of the enzyme – soluble guanylyl cyclase, the NO receptor [2]. The physiology of NO (vaso-relaxation), its synthesis (by nitric oxide synthases NOS1, NOS2, NOS3), catabolism, and targeting, the mechanism of NO action (soluble guanylyl cyclase activation), and the pharmacological role of NO are well studied, especially in the cardiovascular system [1–6]. Due to its high reactivity, NO along with its signaling properties and cytoprotective effects also has the cytotoxic effects when overproduced [7, 8]. NO can act as a cytotoxic effector, when produced at high flux, as a result of inflammatory, stimuli-induced nitric oxide synthase (iNOS) [5, 7]. The cytotoxic effects of NO are largely dependent on the formation of reactive oxidant species, such as nitrogen dioxide, peroxynitrite, alkyl peroxynitrite, dinitrogen trioxide, nitrous acid, and carbonate radical [5] (Fig. 1, B). These reactive species can produce nitration, nitrosation and deamination of DNA bases, which lead to DNA instability.

A



X = H (1)
OH (2)

B

1. $2NO^{\bullet} + O_2 \rightarrow 2NO_2^{\bullet}$
2. $NO^{\bullet} + O_2^{-} \rightarrow ONOO^{-} + CO_2 \rightarrow NO_2^{\bullet} + CO_3^{-\bullet}$
3. $NO^{\bullet} + RO_2^{\bullet} \rightarrow ROONO$
4. $NO^{\bullet} + NO_2^{\bullet} \rightarrow N_2O_3$
5. $NO^{\bullet} + HO^{\bullet} \rightarrow HNO_2$

C

1. $>N–O^{\bullet} + NO_2^{\bullet} \rightarrow >N^{+}=O + NO_2^{-}$
2. $>N–O^{\bullet} + CO_3^{-\bullet} + H^{+} \rightarrow >N^{+}=O + HCO_3^{-}$
3. $>N^{+}=O + ONOO^{-} \rightarrow >N–O^{\bullet} + NO^{\bullet} + O_2$

Fig. 1

On the other hand, aminoxyl (nitroxide) radicals[1] (Fig. 1, A), NO-derived stable free radicals and cell membrane-permeable amphiphiles [9], which can effectively interact with those NO cytotoxic derivatives and recombine with their free radical metabolites [10–12], have been well-known for a long time [13]. The first representative of unique aminoxyl free radicals was synthesized 50 years ago: 1-oxyl-2,2,6,6-tetramethylpiperidine, TEMPO (Fig. 1, A-1) [16]. A common feature of both species – NO and nitroxide (aminoxyl) radicals – is a free radical N–O moiety with a three electron π-bond. Organic compounds of aminoxyl free radicals series are formally originated from the NO species, captured by alkyl substituents, and represent an electronic NO analogue [17]. The extremely high stability of aminoxyl free radicals is due to: (I) the spatial hindrance of the N–O moiety by three saturated alkyl groupings at each alpha-carbon atom, and (II) delocalization of the unpaired electron at N–O bond [9]. While organic substituents of the nitrogen atom are of an aromatic nature or unsaturated, unpaired electron, delocalized *via* an aromatic system, and aminoxyl radicals become unstable, and then easily enter to radical reactions [13]. So, aminoxyls' N–O moiety looses signal properties, when trapped in organic free radical structure, but preserves paramagnetic properties and bioactivity.

[1] The term "nitroxide" was early introduced for this class of free radicals (paramagnetic derivatives of nitric oxide) in the English language literature [13, 14]. Russian scientists also used the terms "iminoxyl" and "nitroxyl" [9, 15]. The correct term for this group of radicals is "aminoxyl" free radicals, as it was stated at the 3rd International Symposium on Spin Trapping and Aminoxyl Radical Chemistry, Kyoto, Japan, 1991, and is a part of on IUPAC convention.

Other features common for both NO and nitroxide (aminoxyl) radicals are their paramagnetic properties and ESR spectrum. Aminoxyl radicals are characterized by the triplet ESR spectrum, while the ESR spectrum of NO species can normally be observed either in the gas phase [18] or after its capture by NO "spin trap" [19]. The aminoxyl ESR spectrum appears to be very sensitive to the properties of microenvironment, which benefits its power in spin labeling studies of biomacromolecules and biomembranes [20, 21]. In the structure of aminoxyl free radicals, the N–O moiety is located in a "sack" formed of alkyl substituents, which makes a signaling function impossible and restricts its reactivity, though retaining its antioxidant properties and biological activity. In general, aminoxyl free radicals facilitate hydrogen peroxide metabolism by catalase-like reaction, dismutate catalytically superoxide anion-radical, and limit the formation of toxic hydroxyl radicals produced by Fenton reactions [14, 11]. It was found that aminoxyl radicals moderate and regulate the bioactivity of NO while neutralizing the toxic products of NO metabolism: peroxynitrite, nitrogen dioxide and carbonate radical [10–12] (Fig. 1, C). Aminoxyls may even down-regulate NO synthase activity [11]. As it follows from detailed studies over the last two decades, aminoxyl bioactivities originate from the ability of the N–O grouping to enter radical and redox reactions [9, 15, 11, 12].

Since aminoxyl free radicals are organic chemical derivatives of NO, they have similar biological activity [15, 11, 12]. As an example, recent findings report in detail that aminoxyl radical TEMPOL [22], 1-oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine (Fig. 1, A-2), caused rapid and reversible dose-dependent reductions in blood pressure, when administered intravenously to hypertensive rodent models [23] (see also US Patent 6096759 of 08.01.2000 – Method for treating essential hypertension). These data confirm numerous and long-term studies of biological activity of aminoxyl radicals, first of all, antineoplastic [24], radiosensitizing [25, 26], radioprotective [9, 27], antiischemic and antishock [28–30], and antiaggregative [31] activities. For the first time, pharmacological – antineoplastic [24] and radiosensitizing [25, 26] – activities of aminoxyl radicals TEMPOL were studied in 1964. Antitumor activity of aminoxyl radicals themselves and aminoxyl derivatives of famous anticancer preparations has been studied in details since then in several laboratories in Europe and in the United States using cell cultures [24], experimental animals carrying solid and ascite tumors [32–41], and in clinics [42]. Aminoxyl radicals were also used as modifiers of antineoplastic therapy, considerably reducing cardiotoxicity of anthracycline antibiotics, as it was demonstrated for spin-labeled rubomicyn – "Emoxyl" [36], or preserving head hairs after irradiation of cancer patients [11]. Antihypertensive effect of TEMPOL, TEMPO (Fig. 1, A), and other aminoxyl free radicals was also accompanied by vasodilation and increased the NO level along with enhanced potassium channel conductance in blood vessels and neurons [23]. The increased NO level in blood as a result of aminoxyl radicals administration in order to decrease high blood pressure does not seem to be caused by the fact that N–O moiety represents a part of aminoxyl radicals [43]: aminoxyls N–O moiety forms covalent bondings with organic substituents (Fig. 1, A-1 and A-2).

Thus, the following biological activities are characteristic of aminoxyl free radicals as NO derivatives: radioprotective [9, 27], antitumor [24, 32–42], antiischemic and antishock [28–30], inhibition of platelet activation [31], haemolytic [44],

neurotropic [45, 46] and some other activities [47–49]. Aminoxyl free radicals have those important types of pharmacological activity, being “nitric oxide like” and possessing very low toxicity [50–52], most likely due to SOD mimic activity of N–O moiety [11, 15]. It has also been shown that aminoxyl radicals neutralize the toxic products of NO metabolism: peroxynitrite, nitrogen dioxide and carbonate radical [10, 12]. This might be important not only for future aminoxyl applications as potent medicines, but also for their applications as complementary medicines (antidotes) to avoid some cytotoxic effects of NO as well. Furthermore, they may be considered to be used as urgent care medicines during natural disasters, technogenic catastrophes or military operations.

On the way of aminoxyl free radicals to clinical trials (e.g., as aminoxyls were applied to treat ocular oxidative/nitrosative stress [53]), particular attention should be paid to the study of their neurologic effects. It was reported [23] that administration of aminoxyl radicals was accompanied by reduced sympathetic nervous system activity at central and peripheral sites. However, a cautionary note has been sounded on influence of aminoxyls on glutamate levels in the hippocampus of conscious rats [46]. Animals injected with aminoxyl of pyrrolidine series showed limbic seizure with secondary generalization. Its administration resulted in neuronal cell loss in CA1 area, which is closely associated with the neurotoxicity of endogenous glutamate and aminoxyl itself [46]. Furthermore, exploring cDNA microarray approach will be important to follow changes in overall gene expression as a result of administration of aminoxyl radicals. Nowadays, this technique has been applied for a number of medicines including NO [54].

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Резюме

Р.И. Жданов, Ф. Мьюрад. Отвечая на вопрос: как использовать аминоксильные (нитроксильные) свободные радикалы для регулирования оксидативного/нитрозативного стресса, а также в качестве потенциальных лекарственных препаратов.

Представлен критический обзор современных способов фармакологического применения аминоксильных (нитроксильных) стабильных свободных радикалов с целью предотвращения цитотоксического воздействия оксидативного и нитрозативного стресса. Как и оксид азота (NO), свободные нитроксильные (аминоксильные) радикалы содержат фрагмент N–O. При помещении в органическую структуру оксид азота теряет свою сигнальную функцию, характеризуется триплетным спектром ЭПР, приобретает способность взаимодействовать с супероксидом и токсичными метаболитами оксида азота, сохраняя при этом некоторые виды биологической активности. Это может стать основой для будущего применения аминоксильных радикалов в фармакологии в качестве противораковых, противолучевых или гипотензивных препаратов. Аминоксильные радикалы рассматриваются как потенциальные лекарства для комплексного применения с индукторами оксида азота с целью избежать цитотоксических эффектов. Для использования аминоксильных свободных радикалов в качестве медицинских препаратов необходимо дополнительное изучение их нейротропных свойств.

Ключевые слова: оксид азота, аминоксильные (нитроксильные) свободные радикалы, сердечно-сосудистая система, сигнализация оксида азота, цитотоксичные метаболиты оксида азота, биоактивность нитроксилов, супероксиддисмутазная активность.

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