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Tempol as an antioxidant; an updated review on current knowledge

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Abstract

An antioxidant is a compound which reduces the oxidation of other molecules. Oxidation is a chemical reaction that can create free radicals, leading to chain reactions that may injure cells, so cause to diseases. Antioxidants end these chain reactions. Investigations have shown tempol can act as an antioxidant. In this review, tempol as supplement antioxidant is introduced for various diseases related to kidney diseases such as chronic kidney disease (CKD) and diabetic nephropathy (DN), etc.

Introduction

In recent years, several evidences show that oxidative stress is closely related to a varied assortment of disorders (1,2). Therefore, it is normally concluded that antioxidants will therefore avert those diseases (2).

The body is ordinarily in a stable state condition with free radicals being continuously produced and reduced. On the other hand, the accumulated long-term destruction done by free radicals is implicated in many degenerative disorders. Evidence from many studies has powerfully implicated oxidative stress in a spectrum of disorders and in the condition of organ dysfunction. Oxidative stress has been exhibited variously as depressed levels of antioxidant materials (for example, vitamin E), dwindling levels of enzymes that form part of the antioxidant advocacy system, and enlarged levels of oxidation produces (for example, DNA damage) (2).

The following is a little list of the states considered to be related to oxidative stress; a damaged immune system and enhanced risk of infectious disorder (3), cancer (4), chronic kidney disease (CKD) (5), diabetes (both insulin-dependent and noninsulin-dependent diabetes (6), diabetic nephropathy (DN) (7), numerous respiratory disorders (8), eye disorder (9), Alzheimer' s disorder (10), schizophrenia (11), intracerebral hemorrhage (ICH) (12), inhibition of oxygen-dependent radiation-induced obesity and hyperlipidemia (13).

Core tip
Tempol administration leads to decrease the intensity of renal dysfunction and damage, DN, ICH, inhibition of oxygen-dependent radiation-induced, and also decrease obesity and hyperlipidemia.

Antioxidants are substances that interrelate with free radicals and neutralize them. The body builds some of the antioxidants which utilizes to neutralize free radicals. These antioxidants are described endogenous antioxidants. Nevertheless, the body depends on external (exogenous) resources, mainly the diet, to reach the rest of the antioxidants which still needed. These exogenous antioxidants are usually named dietetic antioxidants. Grains, vegetables, and fruits are rich resources of dietetic antioxidants. Some dietetic antioxidants are also available as dietetic supplements (14).

Nitroxides can experience one- or two-electron decrease reactions to hydroxylamines or oxammonium cations, correspondingly, they are interconvertible, which provide redox metabolic actions. 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (Tempol) is the most widely examined nitroxide (Figure 1) (15). Tempol is an established piperidine nitroxide and is a water-soluble similarity of the spin label tempo, that is widely active in electron spin resonance spectroscopy (16).

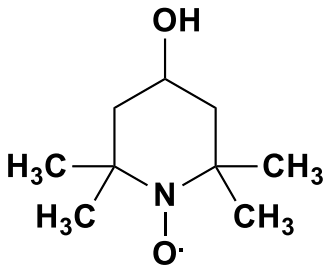

Figure 1. Strucute of tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-N- oxyl).

It has a comparatively low molecular weight (172 g/mol) and infuses biological membranes (17). Furthermore, tempol is a cell membrane-permeable amphilite which dismutates superoxide catalytically, enables hydrogen peroxide metabolism by catalase-like activities, and limits creation of toxic hydroxyl radicals created by fenton reactions. It is approximately effective in detoxifying these reactive oxygen species (ROS) in animal and cell studies (15).

The aim of this review is to examine recent researches into the tempol as an antioxidant on CKD, DN, ICH, inhibition of oxygen-dependent radiation-induced, obesity and hyperlipidemia.

Materials and Methods

For this review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, Web of Science, EBSCO and directory of open access journals (DOAJ). The search was conducted using combination of the following keywords and or their equivalents; tempol, antioxidant, chronic kidney disease, reactive oxygen species, diabetic nephropathy and hydroxyl radicals. Titles and abstracts of review articles, case-control studies, clinical trials, cohort studies, and reports that held relevance to the intended topic were studied too.

Tempol as an antioxidant

As mentioned, nitroxide complexes (for instance; tempol) are stable free radicals which were previously examined in the role of hypoxic cell radio-sensitizers. The stable tempol has lately been shown to care for aerated cells in culture versus superoxide produced from hydrogen peroxide, hypoxanthine/xanthine oxidase, and radiation-persuaded cytotoxicity and to moderately sensitize hypoxic cultured cells (18).

In biochemical researches, tempol has been examined as an agent for controlling ROS by fenton reactions. In the other words, tempol is an effective antioxidant of low molecular weight which has a superoxide dismutase (SOD)-mimic activity, and scavenges superoxide anion ($\cdot O^{2-}$) in vitro and in vivo (15). In brief, it also decreases the creation of hydroxyl radicals either by scavenging superoxide anions or by decreasing the intracellular dilutions of Fe^{2+} and, therefore, the creation of hydroxyl radicals through the fenton or Haber-Weiss reactions (19). Indeed, it presented protective effects in many disorder models counting hypertension (20). In other words, tempol is approximately effective in detoxifying these ROS in cell and animal investigations. When administered intravenously to hypertensive rodent examples, tempol produced rapid and reversible dose- reliant on reductions in blood pressure in 22 of 26 findings. This efficacy was conducted by vasodilation, risen nitric oxide activity, decreased sympathetic nervous system activity at peripheral and central sites, and improved potassium channel conductance in blood neurons and vessels (15). In addition, tempol has been described to prevent ($\cdot O^{2-}$) persuaded damage in different situations f(or example, radiation (21) , inflammation (22) , and cardiac ischemia/reperfusion damage) (23). Additionally, this promising drug reserved ROS creation in vitro better than other antioxidants (20).

Likewise, tempol has been exhibited to protect DNA (24), lipids (25), or proteins (26) from oxidative damage. Tempol interrelated with other antioxidants to endorse their ability to decrease oxidized lipids (27). Equally important, nitroxides avoided oxidative injury in many cellular or organ systems. For instance, in the skin following UV radiation (28) in tissues following incubation in a great glucose-containing medium (29), or in cells following x-irradiation (30).

Tempol effects on chronic kidney disease

CKD is a sluggish, progressive and irreparable injury of renal function. The pathogenesis of CKD in most instances involves a complex interface of inflammatory and hemodynamic procedures that directs to end-stage renal disease (ESRD) distinguished by glomerulosclerosis, tubulointerstitial fibrosis and the complete damage of renal function (31).

Oxidative stress has been associated in the pathogenesis of CKD and antioxidants may better disorder progression (5). Furthermore, oxidative stress is a significant feature of CKD and a main mediator of its problems (32). ROS play an major role in standard cellular physiology (5). ROS are significant for the pathogenesis of CKD and antioxidants may sluggish or prevent disorder progression (33). Nitroxides apply redox metabolic activities and tempol is the most widely studied nitroxide (20). Tempol is effectual in detoxifying ROS in cell and animal investigations (19). Management of tempol has multiple influences on kidney. Available information on the effect of management of tempol on progression of CKD are partial (5). However, so far, there has been comparatively little investigation into any protective activities given by tempol within the kidney or in individual renal structures for example the proximal tubules, interstitial area, vessels and glomeruli, under pathophysiologic or normal situations.

In 1999, Schnackenberg and Wilcox published a paper in which they described how a 2-week management of tempol decreased both hypertension and renal excretion of eight-iso-prostaglandin F2a (consumed as a sign of oxidative stress) in spontaneously hypertensive rats (SHRs) (34). Additionally, Leach et al detected that tempol reduces

renal dysfunction and damage produced by endotoxin in the rat (35) and all through hemorrhagic shock (36). The pathogenesis of entity includes an improved formation of ROS (37). In addition, they have also demonstrated that tempol decreases infarct size in rodent patterns of area myocardial ischemia/reperfusion (36).

Tempol effects on diabetic nephropathy

DN or diabetic kidney disease (38) is a progressive kidney disorder produced by destruction to the capillaries in the kidneys' glomeruli, and tubulointerstitial area (39). It is detected by decreased renal function and dispersed scarring of the glomeruli. It is mostly owing to longstanding diabetes mellitus or hypertension, and is a major reason for dialysis in numerous developed countries (40).

Diabetic kidney disease is the most common reason of the CKD throughout the world. Oxidative stress on the other hand has a main and well identified role in its pathophysiology (41). Accordingly the majority of patients with type I or II diabetes mellitus (DM) develop nephropathy after a cryptographic period of about 15 years. It is categorized by proteinuria, decreased glomerular filtration rate (GFR), podocyte damage, mesangial matrix collection and tubulointerstitial injury (42). Oxidative stress has a main role in diabetes complications counting diabetic kidney disease (7). A developing amount of evidence shows that antioxidant capability is reduced in diabetic patients (43). Animal and clinical investigations have verified that antioxidant therapy plays an effective role in decreasing the development of diabetic kidney disease (44) glutathione peroxidase (GPx). In fact, SOD and catalase and total antioxidant capacity (TAC) were significantly reduced in both type I and type II diabetic groups, with and without nephropathy. In contrast with normal healthy individuals (45), the TAC reduction is coordinated with intensity of microalbuminuria too (46). Also, SOD enzyme is upregulated in answer to arise in oxidative stress (47). This is a significant cellular defense process. Thus decrease of SOD enzyme in the diabetic condition causes renal cell damage. Active diabetic mice had considerably higher serum SOD compared with inactive littermates (48). Several examinations have investigated SOD action and expression. A number of, but not all of them, appeared upregulated renal SOD action (49). Tempol, a SOD simulated, is a recognized anti-oxidative agent and has been examined extensively in animal type. Tempol prevented the impression of glucose on rat glomerular mesangial cells to produce vascular endothelial growth factor (50). Cu/Zn SOD smash mice developed more intense nephropathy following induction of DM which was decreased by oral tempol (51). Equally important, tempol management to obese, hypertensive Zucker rats, decreased renal inflammation and magnitude fibrosis but failed to decrease the proteinuria (52). Other examinations, on the contrary, showed decrease of proteinuria by tempol management (53).

In 2016, Ranjbar et al observed a rise of oxidative stress biomarkers (for example GPx, SOD, lipid peroxidation and catalase) after induction of diabetes in mice. They detected decrease of proteinuria by tempol management. They concluded that tempol can improve diabetic kidney disorder (41).

Tempol effects on alleviates intracerebral hemorrhage

ICH explanations for about 10-15 percent of strokes in Western countries (54) and equal to 20-30 percent in Asian countries (55). ICH is the most unsuccessful stroke subtype as it is correlated to high mortality, poor clinical result, and less effectual remedial options other than stroke subtypes (56).

In fact, nitric oxide has a variation of functions in physiological systems, mainly in the vasculature and the central nervous system (57). Additionally, asymmetric dimethylarginine nitric oxide, and nitric oxide synthase are increasingly correlated with ischemic stroke. However, whether these complexes also affect the procedure and result of ICH is not clear yet (57).

ICH-induced brain damage runs to irreversible disturbance of the blood–brain barrier (BBB) and mortality brain edema with enormous cell death. Even though secondary injury could, in cause, be avoidable, no effective therapy approaches currently occur for patients with ICH. Tempol, a catalytic forager of peroxynitrite ($ONOO^-$) derivative free radicals, has been confirmed to ameliorate brain damage in some types of brain insults (58). In 2015, Wanyong et al (12) described potential neuroprotective influence of tempol after collagenase-induced ICH in rats, then tempol was given immediately later ICH. The properties of tempol on ICH were estimated by measuring brain edema, neurological deficits, apoptotic cell death, and BBB permeability. In addition, the procedures of act of tempol, with its clear capability on the derived of $ONOO^-$ (3-nitrotyrosine (3-NT), $ONOO^-$, and its derived -mediated nitration marker) and expression of stretched junction protein (zonula occludens-1 [ZO-1]), were likewise examined. Perihematomal 3-NT risen significantly keep to ICH and expressed round vessels accompanied by decreased and irregular expression of ZO-1. Tempol therapy considerably suppressed 3-NT creation and preserved ZO-1 levels, and directed to improvement in neurological results and reduction of brain edema, BBB leakiness, and apoptosis (12). They concluded that tempol has neuroprotective capacity in experimental ICH and may facilitate combat ICH-induced brain damage in patients (12).

Tempol effects on inhibition of oxygen-dependent radiation induced

The adverse effects of ionizing radiation contain mutagenesis, cytotoxicity, and carcinogenesis. In 1940, the first finding on capability of sulfhydryls (thiols), such as cysteamine and cysteine, to present radiation defense to animals made interest to find substances had protective efficacy against radiation- caused cytotoxicity (59). It seems that, radiation harms biomolecules, in great

part (around 80%), via its interplay with water to create H_2O_2 and free radicals, or via interaction with oxygen to create the superoxide anion ($\cdot O_2^-$). Thiols, which perform by contribution of a hydrogen atom to hurt molecules or by "scavenging" radiation-induce free radicals, induced significant defense to animals (59). In spite of extensive analysis and synthetic attempts, no thiol-created radioprotector has been made to be considerably better than cysteamine.

In 1989, Samuni et al demonstrated SOD mimetic activity (60) which had the capability to defense mammalian cells from destruction by superoxide produced by hydrogen peroxide and by hypoxanthine/xanthine oxidase (61). In this regards, Mitchell et al found that tempol protect cells against ionizing radiation and may be encountered as a fundamental modality to ameliorate radiation caused cellular injury (21).

Tempol effects on obesity and hyperlipidemia

Dyslipidemia has a major role in many cardiovascular disease involving atherosclerosis (62). Low-density lipoprotein-cholesterol (LDL-C) and total blood cholesterol are well-established risks, and classified factors, for cardiovascular disorders (62).

Therapeutic decrease of high-risk lipid parts are strongly related to improved results. However, inhibition and therapy of obesity (by behavioral change, pharmaceuticals or surgical methods), leads to decrease the onset of dyslipidemia and resultant injuries (62). One choice is the stable nitroxide free radical tempol which has been proved to modulate radiation, injury and tumorigenesis (13).

In 2015, Kim et al described addition of tempol to the diet considerably diminished the increase in body mass of high fat diet-fed mice to levels like to those of the chow-fed mice. They also described plasma triglyceride (total cholesterol), LDL-C and HDL-C levels were considerably elevated in plasma from the high fat diet-fed (HFD-fed) associated with chow -fed mice then tempol treated. Tempol reduced this elevation. Additionally, interleukin-6 levels were considerably elevated in the HFD-fed, contrasted to the food-fed, animals, and this rise was markedly reduced by tempol. A resemble pattern of variations was discovered for the inflammatory markers like myeloperoxidase and serum amyloid A, with tempol-supplementation, while it considerably blunting the rises detected in the HFD-fed, contrasted to chow-fed animals (63).

In other words, these information designate that in a well-established model of obesity- related to hyperlipidemia, tempol had a considerable impact on hyperlipidemia, and body mass.

Discussion

As a matter of fact, several evidences have shown in vivo and in vitro investigations that, ROS plays an main role in the pathophysiology of renal ischemia/reperfusion damage, DN, and ICH (64).

Earlier studies have shown that tempol can act as a protective agent versus oxidative injury in multiple pathologies (65) and is not able to influence cell growth or produce toxicity at 1 mM in cell medium (66) or at 10 mg/g nutrition in animal investigations (~58 mM) (13). In fact, tempol is a SOD derivative that belongs to a group of non-thiol including radiation protectors, and has the capability to infuse the membrane (67). On the whole, beneficial influences of tempol observed in this review are owing to its capability to decrease the generation or the influences of hydroxyl radicals (37).

Conclusion

This article shows that tempol administration leads to decrease the intensity of renal dysfunction and damage, DN, ICH, inhibition of oxygen-dependent radiation-induced, and also decrease obesity and hyperlipidemia.

Authors' contribution

HN and SBR wrote the paper equally.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

The authors of this manuscript declare that they all have followed the ethical requirements for this communication. Also, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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