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ORIGINAL ARTICLE

Tempol improves lipid profile and prevents left ventricular hypertrophy in LDL receptor gene knockout (LDLr-/-) mice on a high-fat diet

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KEYWORDS
Nitroxides;
Tempol;
Dyslipidemia;
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Abstract
Introduction and Objective: Dyslipidemia is associated with increased risk of cardiovascular disease and atherosclerosis, and hence with high morbidity and mortality. This study investigated the effects of the nitroxide 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl (Tempol) on lipid profile and cardiac morphology in low-density lipoprotein (LDL) receptor gene knockout (LDLr-/-) mice.
Methods: Male LDLr-/- mice (three months old, approximately 22 g weight) were divided into the following groups: controls, including (1) standard chow (SC, n=8) and (2) high-fat diet (HFD, n=8); and treatment, including (3) standard chow + Tempol (SC+T, n=8) (30 mg/kg administered by gavage, once daily) and (4) high-fat diet + Tempol (HFD+T, n=8) (30 mg/kg). After 30 days of the diet/treatment, whole blood was collected for analysis of biochemical parameters (total cholesterol, triglycerides [TG], high-density lipoprotein [HDL], LDL, and very low-density lipoprotein [VLDL]). The heart was removed through thoracotomy and histological analysis of the left ventricle was performed.
Results: A significant increase in TG, LDL, and VLDL and marked left ventricular hypertrophy (LVH) were demonstrated in the HFD group relative to the SC group ($p<0.05$), while Tempol treatment (HFD+T group) significantly ($p<0.05$) prevented increases in the levels of these lipid profile markers and attenuated LVH compared with the HFD group.

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Conclusion: In this study, Tempol showed potential for the prevention of events related to serious diseases of the cardiovascular system.

PALAVRAS-CHAVE
Nitróxidos;
Tempol;
Dislipidemia;
Hipertrofia ventricular esquerda;
EROs/ERNs

Tempol melhora o perfil lipídico e previne a hipertrofia ventricular esquerda em camundongos nocaute para o gene do receptor de LDL (LDL-/-) sob uma dieta hiperlipídica

Resumo
Introdução e objetivo: A dislipidemia está associada com aumento do risco para as doenças cardiovasculares e aterosclerose, refletindo na alta morbidade e mortalidade associadas. Este estudo investigou os efeitos do nitróxido *4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl* (tempol) sobre o perfil lipídico e a morfologia cardíaca em camundongos nocaute para o gene do receptor da lipoproteína de baixa densidade (LDLR KO ou LDL-/-).
Métodos: Camundongos machos (três meses de idade, pesando aproximadamente 22 g) foram divididos nos seguintes grupos: grupos controlo: (1) ração padrão ([RP] n=8) = camundongos LDL-/- + dieta padrão; (2) dieta rica em lipídios ([DRL] n=8) = camundongos LDL-/- + DRL; e grupos tratados: (3) RP + tempol (RP + T, n=8) = camundongos LDL-/- + dieta padrão + tempol (30 mg/kg, administrado por gavagem, uma vez por dia); (4) DRL + tempol (DRL + T, n=8) = camundongos LDL-/- + DRL + tempol (30 mg/kg). Após 30 dias de dieta/tratamento, o sangue total foi obtido para análise dos parâmetros bioquímicos (colesterol total [CT], triglicerídeos [TG], HDL, LDL e VLDL) e, através de uma toracotomia, o coração foi removido e uma análise histológica do ventrículo esquerdo foi realizada.
Resultados: Foi demonstrado um aumento significativo dos níveis de TG, LDL e VLDL, bem como uma considerável hipertrofia ventricular esquerda (HVE), no grupo DRL em comparação com o grupo RP ($p<0,05$); o tratamento com tempol (grupo DRL + T) preveniu significativamente ($p<0,05$) o aumento nos níveis destes marcadores de perfil lipídico e atenuou a HVE, em comparação com o grupo DRL.
Conclusão: Tempol apresentou potencial para a prevenção de eventos que podem levar a graves doenças do sistema cardiovascular.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality and is responsible for approximately 30% of all deaths, claiming approximately 17 million lives per year worldwide in 2012.[1–3] Furthermore, many studies have firmly established the relationship between cardiovascular disease and metabolic disorders and underlying conditions such as dyslipidemia, diabetes, and hypertension.[4–8]

Dyslipidemia and associated atherosclerotic/cardiovascular events can present with intense inflammation and increased production of reactive oxygen/nitrogen species (ROS/RNS) from mitochondrial oxidative stress and/or the NADPH oxidase complex, which can cause oxidative modification of LDL, thus amplifying the inflammatory potential (i.e., recruitment of phagocytes and activation of the neutrophil oxidase [Nox]-2 system) and proatherogenic events. Moreover, uncontrolled dyslipidemia can have serious consequences for the cardiovascular system, resulting in morphological changes (left ventricular hypertrophy [LVH]), dysfunction, and even heart failure.[9–16]

Regulation of lipid metabolism is an important target for therapeutic intervention in dyslipidemic processes to prevent or reduce the risk or severity of cardiovascular disease, and appropriate intervention can have an impact on its clinical course. However, due to the high cost, prolonged use, and especially the adverse effects associated with some lipid-lowering drugs, a drug to control dyslipidemia that presents fewer side effects and a better cost/benefit ratio is highly desirable.[17–19]

Studies have explored other compounds with antioxidant properties in the prevention of cardiovascular disease.[10,20] Over the last few decades, nitroxides have been widely investigated because of their antioxidant capabilities.[20–22] Among them, 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl (Tempol) is a superoxide dismutase (SOD) mimetic that shows a good partition coefficient, interacts with a broad spectrum of oxidants produced in the human body, and is able to break the chain of redox reactions.[21,23,24]