Communication

http://dx.doi.org/10.1590/1981-86372025002220250003

Revista Gaúcha de Odontologia

Nitric oxide in oral homeostasis: endogenous production and microbiota contribution

Óxido nítrico na homeostase bucal: produção endógena e contribuição da microbiota

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ABSTRACT

Nitric oxide plays a crucial role in oral homeostasis, yet its relevance remains underexplored. This communication aims to describe the dual role of nitric oxide in oral health by examining its endogenous production by adult odontoblasts and its generation by nitrate-reducing bacteria in the oral microbiota. Additionally, it presents therapeutic approaches to modulate nitric oxide levels, including nitric oxide-releasing biomaterials and dietary interventions such as prebiotics and probiotics. Recent findings confirm the constitutive expression of nitric oxide synthase in healthy adult odontoblasts, indicating a continuous role in pulp health maintenance. Simultaneously, nitrate-reducing bacteria contribute to oral balance by

How to cite this article

Silva AB, Carvalho PI, Guillo LA. Nitric oxide in oral homeostasis: endogenous production and microbiota contribution. RGO, Rev Gaúch Odontol. 2025;73:e20250022. http://dx.doi.org/10.1590/1981-86372025002220250003

artigo alinhado ao objetivo Boa saúde e Bem-estar dos Objetivos de Desenvolvimento Sustentável (ODS)

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metabolizing dietary nitrates into nitric oxide. These mechanisms support nitric oxide as a key modulator of oral homeostasis. Understanding and leveraging these pathways may provide innovative strategies for oral disease prevention and tissue regeneration, reinforcing the importance of nitric oxide-targeted therapies in dentistry.

Indexing terms: Homeostasis. Mouth. Nitric oxide.

RESUMO

O óxido nítrico desempenha um papel crucial na homeostase oral, porém sua relevância ainda é pouco explorada. Esta comunicação tem como objetivo descrever a dupla função do óxido nítrico na saúde bucal, examinando sua produção endógena por odontoblastos adultos e sua geração por bactérias redutoras de nitrato na microbiota oral. Além disso, apresenta abordagens terapêuticas para modular os níveis de óxido nítrico, incluindo biomateriais liberadores de óxido nítrico e intervenções dietéticas, como prebióticos e probióticos. Descobertas recentes confirmam a expressão constitutiva da enzima óxido nítrico sintase em odontoblastos adultos saudáveis, indicando um papel contínuo na manutenção da saúde pulpar. Simultaneamente, as bactérias redutoras de nitrato contribuem para o equilíbrio oral ao metabolizar nitratos da dieta em óxido nítrico. Esses mecanismos posicionam o óxido nítrico como um modulador essencial da homeostase oral. Compreender e explorar essas vias pode fornecer estratégias inovadoras para a prevenção de doenças bucais e regeneração tecidual, reforçando a importância de terapias direcionadas ao óxido nítrico na odontologia.

Termos de indexação: Homeostase. Boca. Oxido nítrico.

INTRODUCTION

The maintenance of oral health should be a consistent practice throughout all stages of life, as it is a fundamental component of general homeostasis [1]. However, attention to these practices often intensifies only in the presence of pathological conditions, such as caries, cracks, or periodontal diseases.

In this text, we highlight Nitric Oxide (NO), an essential bioactive molecule that, although widely recognized for its beneficial functions in systems such as the cardiovascular and nervous systems, still has a role in the context of the oral cavity that is frequently underestimated.

In endothelial cells and neurons, where the continuous production of NO (at picomolar concentrations) is mediated by the enzyme Nitric Oxide Synthase (NOS), NO regulates fundamental processes such as vascular tone, platelet aggregation, angiogenesis, and neurotransmission [2]. These events reflect the direct interaction of NO with the iron atom in the heme group of proteins like soluble Guanylate Cyclase (sGC), which stimulates the production of cyclic GMP (cGMP), a molecule responsible for triggering the observed beneficial effects [3].

However, in the context of oral health, the role of NO remains underexplored beyond its antimicrobial properties and its involvement in the inflammatory response of dentin-pulp complex and periapical tissues [4,5].

Therefore, this communication aims to describe the role of NO in oral homeostasis by examining its endogenous production by adult odontoblasts and its generation by nitrate-reducing bacteria in the oral microbiota. Furthermore, it discusses therapeutic strategies to modulate NO availability, including NO-releasing biomaterials and dietary interventions such as prebiotics and probiotics.

NO in the healthy oral cavity

Production by adult odontoblasts

In humans, there is evidence that NOS may be constitutively present in sensory nerve fibers (originating from branches of the trigeminal nerve) [6]. Also, the levels of NOS enzyme expression increase in the more advanced stages of odontogenesis, and its presence in clusters of stellate reticulum cells, ameloblasts and odontoblasts has been confirmed, during the germinative development of deciduous or permanent teeth [7]. Thus, NO would be responsible for mediating cell proliferation and differentiation events at the stage of tooth formation.

However, the discovery of the constitutive expression of NOS in adult odontoblasts of healthy dental pulp [8], suggests that these cells not only play a crucial role in odontogenesis. This finding also allows us to consider that odontoblasts may be involved in maintaining pulp tissue health throughout life. Such a discovery has important implications for therapeutic approaches such as Vital Pulp Therapy (VPT) or even pulp-dentin regeneration, which aim to preserve or reconstruct lost pulp and dentin tissue [9,10].

Until recently, these treatment modalities have been based on the regenerative capacity of pulpal stem cells and, as a result, several biomaterials unrelated to NO are under development [11,12]. However, more recently, limited studies have investigated the use of NO donor compounds or biomaterials with controlled release of NO, mainly exploring the antimicrobial, immunomodulatory and revascularization-promoting properties in injured pulp regions [13-15]. A study with adult dogs, focused on the regeneration of the pulp-dentin complex, a NO-releasing gel demonstrated to stimulate angiogenesis and also promote the appearance of odontoblast-like cells [16], suggesting in our view, the potential of NO to stimulate the differentiation of stem cells into odontoblasts, which can continue to produce NO constitutively, contributing to the maintenance of pulp health.

Production by nitrate-reducing bacteria

In addition to the endogenous production of NO by adult odontoblasts, the oral microbiota also plays an essential role in metabolizing nitrates present in the diet, directly contributing to the maintenance of a balanced oral environment. Studies show that sodium nitrate solutions increase eubiosis and reduce dysbiosis in *in vitro* biofilm models, while topical use of nitrate gels can potentiate these effects, indicating a new approach to periodontal treatments [17]. Currently, the intake of nitrate as a prebiotic, probiotics or dietary modification represent new possibilities in the prevention of caries [18-20].

CONCLUSION

The dual contribution of NO to oral health – one endogenous, mediated by odontoblasts, and the other microbial, generated by nitrate-reducing bacteria – illustrates the complex interaction between dental tissues and the oral microbiota in maintaining homeostasis. Recent evidence supporting the constitutive expression of NOS in adult odontoblasts reinforces their continuous role in pulp tissue health, extending beyond odontogenesis. Additionally, the ability of the oral microbiota to generate NO highlights the potential of dietary nitrates, prebiotics, and probiotics in promoting a balanced oral environment. Given these findings, strategies that preserve or stimulate NO-mediated processes, including NO-releasing

biomaterials and nutritional interventions, may represent significant advances in oral health promotion and future therapeutic applications in dentistry.

CLINICAL PERSPECTIVES

NO donor substances, NO-releasing biomaterials, nitrate-rich foods, aqueous sodium nitrate solutions, and probiotics represent innovative interventions for dental practice. For example, advanced biomaterials with controlled release of NO are being developed to stimulate pulp regeneration, while the use of topical gels with nitrate has shown potential in periodontal treatments by improving the eubiosis of the oral microbiota. Additionally, diets that encourage the consumption of nitrate-rich foods and the use of probiotics can play a central role in preventing cavities and maintaining a balanced oral environment. Understanding the multifaceted role of NO, both as an endogenous mediator and as a result of the beneficial activity of the oral microbiota, is essential to expand its application in innovative therapeutic approaches in dentistry.

Conflict of interest: The authors declare that there are no conflicts of interest.

Collaborators

AB Silva, PI Carvalho, conceptualization, writing – original draft. LA Guillo, conceptualization project administration, supervision, writing- original draft, writing – review and editing.

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Received on: 8/1/2025
Final version resubmitted on: 7/3/2025
Approved on: 24/4/2025

Assistant editor: Luciana Butini Oliveira