Japanese Dental Science Review (2010) **46**, 11—16

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jdsr

REVIEW ARTICLE

# Drug-induced gingival overgrowth and its tentative pharmacotherapy

**Hiroko Matsumoto [a,b], Reiri Takeuchi [a], Makiko Ono [c], Yoshiaki Akimoto [b,c], Naomi Kobayashi [d], Akira Fujii [d,e,*]**

[a] *Department of Oral Molecular Pharmacology, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba 271-8587, Japan*
[b] *Research Institute of Oral Science, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba 271-8587, Japan*
[c] *Department of Oral Surgery, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba 271-8587, Japan*
[d] *Department of Clinical Pharmacology, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba 271-8587, Japan*
[e] *Research Institute of Oral Science, University Research Center, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba 271-8587, Japan*

Received 30 July 2009; accepted 2 September 2009

**KEYWORDS**
Nifedipine;
Tenidap;
18α-Glycyrrhetinic acid;
Gingival fibroblasts;
Cell cycle

**Summary** The characters in gingival fibroblasts derived from a nifedipine-reactive patient (nifedipine responder: NIFr) and those from a nifedipine-nonreactive patient (nifedipine non-responder: NIFn) are summarized, and investigated a possibility of tenidap, (±)-5-chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, and 18α-glycyrrhetinic acid (18α-GA) as a therapeutics for gingival overgrowth caused by calcium channel blockers. Tenidap discharges intracellular $Ca^{2+}$ store, resulting in a depletion of intracellular $Ca^{2+}$ store in cultured human gingival fibroblasts. It also inhibited cell growth, DNA and collagen syntheses, lowered intracellular pH in nicardipine responder cells, and enhanced matrix metalloproteinase-1 formation in NIFr cells. 18α-GA inhibited cell proliferation and $G_1$/S transition induced in NIFr cells. It was also shown that cell cycle control proteins were down-stream targets in the growth-inhibition activity of 18α-GA in NIFr cells. These results suggest that tenidap and 18α-GA might be effective for the prevention of gingival overgrowth caused by calcium channel blockers.


**Contents**



* Corresponding author at: Department of Clinical Pharmacology, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba 271-8587, Japan. Tel.: +81 47 360 9559; fax: +81 47 360 9560.
*E-mail address:* fujii.akira27@nihon-u.ac.jp (A. Fujii).

1882-7616/$ — see front matter 
doi:10.1016/j.jdsr.2009.09.001

## 1. Introduction

Gingival overgrowth in response to anti-epileptics (phenytoin and sodium valproate), immunosuppressants (cyclosporine A), and calcium channel blockers (nifedipine, diltiazem, verapamil, nicardipine, amlodipine, manidipine, and nisoldipine) is well-recognized. Particularly, many case reports have implicated nifedipine (NIF), one of the dihydropyridine calcium channel blockers, as a cause of gingival overgrowth (first reported by Ramon et al. [1] and Lederman et al. [2]). The incidence of gingival overgrowth due to NIF has been reported to be 6.5% [3], 7.6% [4], more than 10% [5], 11.6% [6], 15% [7], and 20% [8]. We also reported the incidences of gingival overgrowth caused by amlodipine, diltiazem, manidipine, nicardipine, and nisoldipine were 1.1%, 4.1%, 1.8%, 0.5%, and 1.1%, respectively [4]. However, the mechanism of the NIF-induced gingival overgrowth has not been well clarified. We have previously demonstrated the difference on cell growth, collagen synthesis, calcium response, intracellular crosstalk, and cell cycle between gingival fibroblasts derived from a NIF-reactive patient (NIF responder, NIFr) and those from a NIF-nonreactive patient (NIF non-responder, NIFn).

In this review, the specific characters in NIFr and NIFn are summarized, and a possibility of tenidap, (±)-5-chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, and 18α-glycyrrhetinic acid (18α-GA) was investigated as a therapeutics for gingival overgrowth caused by calcium channel blockers.

## 2. Characterize NIFr and NIFn cells

### 2.1. Response to calcium channel blockers on proliferation, DNA and collagen syntheses

In general, the histological examination of the gingival specimens from patients reactive to NIF medication revealed large bundles of dense collagenous fivers with a moderate increase of fibroblasts in addition to epithelial hyperplasia with acanthosis and parakeratosis, and elongation of the rete pegs. Thus, it was thought interesting to focus on gingival fibroblasts obtained from NIFr and NIFn. As the first step of the investigation, the difference between NIFr cells and NIFn cells was studied. NIFr cells exhibited greater proliferation rates and DNA and collagen syntheses than NIFn cells in the presence of 1 μM of calcium channel blockers (nifedipine, diltiazem, nicardipine, and verapamil) or phenytoin [9]. Therefore, it is possible that gingival fibroblasts from NIF-reactive patients may be also susceptible to the other calcium channel blockers, which indicates that those patients who developed gingival overgrowth because of NIF medication may also develop it in response to other calcium channel blockers. This was confirmed later, but not for nisoldipine responder cells [10]. Thus, fibroblasts from patients reactive to NIF and nicardipine medication gave a better cell proliferation rate, DNA synthesis, and an increased number of EGF receptors compared to non-drug-treated control, but not in fibroblasts from patients reactive to nisoldipine medication. In general, the presence of tooth and gingival crevice are essential to generate drug-induced gingival overgrowth, suggesting that the presence of gingival crevicular fluid might be important for gingival overgrowth. Interleukin-1α (IL-1α) predominates in gingival crevicular fluid and greater amount of NIF is found in gingival crevicular fluid in the patients with periodontal disease, it was interesting to investigate the simultaneous effect of NIF and IL-1α on cell proliferation and DNA synthesis. The presence of IL-1α resulted in greater cell proliferation and DNA synthesis than in the presence of NIF alone and NIFr cells showed greater response. The DNA synthesis rate with a combination of NIF and IL-1α was also higher than that for NIF or IL-1α alone. Thus, the interaction between NIF and gingival inflammation might play an important role in the pathogenesis of NIF-induced gingival overgrowth [11]. IL-1α also yielded significantly higher basic fibroblast growth factor (bFGF) production and release, and also enhanced bFGF mRNA expression. In addition, levels of released bFGF were significantly higher in cells pretreated with IL-1α, followed by bradykinin and thapsigargin in the presence of extracellular $Ca^{2+}$. The transient mobilization of intracellular $Ca^{2+}$ accelerated the release of bFGF in IL-1α-pretreated cells, but not in untreated cells [12]. These findings suggest that NIFr cells are more sensitive to NIF and that IL-1α accelerate this sensitivity through bFGF formation.

### 2.2. Response to stimulants on intracellular free $Ca^{2+}$ concentration

The cell proliferation in cultured fibroblasts involves a sequence of biochemical events, which begin in part at the cell surface by mitogen stimulation and progress temporally and spatially to the cell nucleus through signal transduction pathways. Among the earliest of these events are dramatic changes in intracellular free $Ca^{2+}$ concentration in a variety of cell types via a direct effect of inositol 1,4,5-trisphosphate ($IP_3$) on the ligand-activated calcium channels in intracellular $Ca^{2+}$-storing organelles [13,14]. Therefore, it was interesting to investigate if there are any differences between NIFr cells and NIFn cells against the stimulants, such as bradykinin, thrombin, histamine, bombesin, prostaglandins $E_2$ and $F_{2\alpha}$, and platelet derived growth factor-BB. NIFn cells showed a greater cytosolic calcium response to bradykinin, thrombin, prostaglandins $E_2$ and $F_{2\alpha}$ and platelet derived growth factor-BB than NIFr cells. On the contrary,