

# NNK가

\* .      \*\* .      \* .      \* .      \* .      \*

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\*\*

I.      Nicotinana alkaloids      N -

   Nitrosonor - nicotine (NNN)      (4 -

   Methylnitrosamino) - 1 - (3 - pyridyl) - 1 -

   butanone (nicotine - derived nitrosamino -

   ketone: NNK)

   . Kawano

nitrosamines,      , hydrogen      NNK가 K - ras      10),

cyanide      가

   가      11, 12),

   가      13 - 16)

Fang      1)      17)

alkaline phosphatase      가      가      15

   . Mark<sup>2)</sup>

   가      18) Bastiaan<sup>19)</sup>

, David      3)

   . Alpar      4)

   Feldmen      20)

   가      가      21, 22),

   Preber      23)

5, 6) B - cell      T - cell      가      T - cell

   7, 8),

Nils      9)      6, 24, 25),

nicotne NNK medium( - MEM)# 100% , 5%  
 CO<sub>2</sub> 가 37 가 \$  
 . 75cm<sup>2</sup>  
 MTT test 가 7 - 10  
 .  
 II. 4 - 5  
 .  
 1. (2) MTT test  
 (1) \* MTT(microtiter assay which uses  
 98% the tetrazolium salt)\*  
 , 50ng/ml, 100ng/ml Tetrazolium salts  
 .  
 (2) nicotine - derived nitrosaminoketone( MTT test succi -  
 NNK)\*\* nate dehydrogenase inhibition(SDI)  
 ( 4 - Methylnitrosamino) - 1 - ( 3 - SDI  
 pyridyl) - 1 - butanone 0.9% NaCl MTT가 formazan salt  
 50ng/ml for -  
 100ng/ml .  
 2. 96 - well  
 , NNK  
 MTT test 530nm  
 (1) .  
 20 가  
 1 × 1mm<sup>2</sup> .  
 HBSS(Hank's Balanced Salt 96 - well plate well 가  
 Solution)# 1000rpm 5000 가 , trypsin  
 5 3 . HBSS EDTA flask  
 25cm flask 1 - 2ml 20% fetal trypan - blue hemocytometer  
 bovine serum(FBS)#, 100unit/Mℓ penicillin,  
 100mg/Mℓ streptomycin, 0.5mg/Mℓ ampho -  
 tericin - B#가 - minimal essential well .  
 96 - well plate 48 -

\* : Sigma Chemical Co., Mi., U.S.A.

\*\* : TCR Toronto Research Chemicals Inc.

# : Gibco/BRL Scientific Technologies Inc., U.S.A.

\$ : Infrared CO<sub>2</sub> incubator, Forma Scientific Inc., U.S.A.

\$\$ : Model ETY - 96, Toyo instrument Inc., Tokyo, Japan.

well  
 50ng/ml,100ng/ml  
 NNK  
 48 - well  
 plate 30 , 60 , 90  
 , 120 , 240 37  
 3 - (4,5 - dimethylthiazole - 2 - yl) - 2,  
 5 - diphenyl tetrazolium bromide(MTT)  
 100μl well 가 2 37 NNK 3 24,  
 . MTT 100μl 48, 72, 96, 144 MTT test  
 dimethyl Sulfoxide(DMSO)\* 가  
 formazan ELISA  
 reader\$\$ 530nm (4)

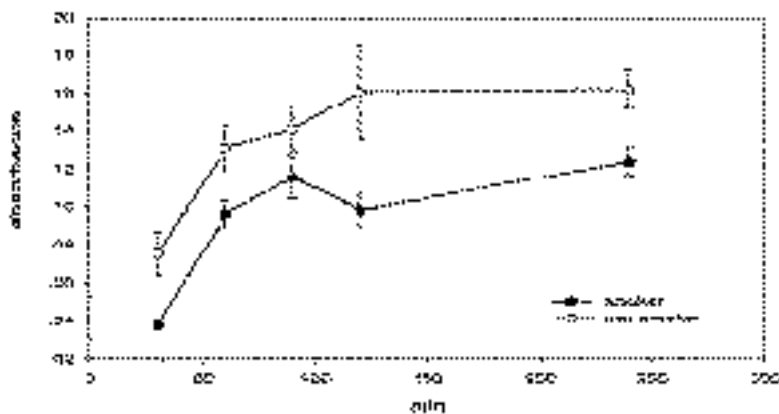


Figure 1. The comparison of attachment between non - smoker and smoker's gingival fibroblast

Table 1. The comparison of attachment between non - smoker and smoker's gingival fibroblast

attachment control	non - smoker	smoker
30 min	0.075 ± 0.011	0.037 ± 0.003*
60 min	0.131 ± 0.011	0.096 ± 0.007*
90 min	0.140 ± 0.012	0.115 ± 0.011*
120 min	0.160 ± 0.024	0.098 ± 0.008*
240 min	0.162 ± 0.010	0.124 ± 0.007*

\*: Statistically significant different from non - smoker group(P<0.05)

and Whitney test Mann 가

III. (P<0.05).

1. 2. NNK

Figure 1 Table 1

가 가 NNK 50, 100ng/ml  
가 Figure 3 Table 3  
120

plateu (P<0.05). Figure (P<0.05).

2 Table 2

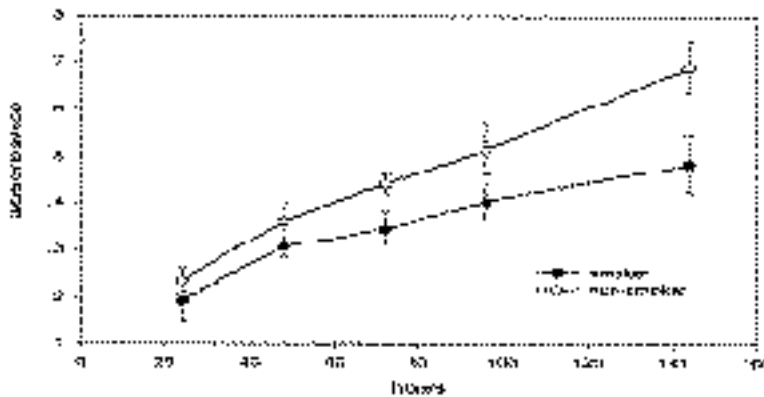


Figure 2. The comparison of growth between non - smoker and smoker's gingival fibroblast

Table 2. The comparison of growth between non - smoker and smoker's gingival fibroblast

growth control	non - smoker	smoker
24 hr	0.213 ± 0.013	0.233 ± 0.030
48 hr	0.332 ± 0.016	0.291 ± 0.015*
72 hr	0.453 ± 0.027	0.316 ± 0.020*
96 hr	0.550 ± 0.029	0.394 ± 0.052*
144 hr	0.728 ± 0.027	0.527 ± 0.031*

\*: Statistically significant different from non - smoker group(P<0.05)

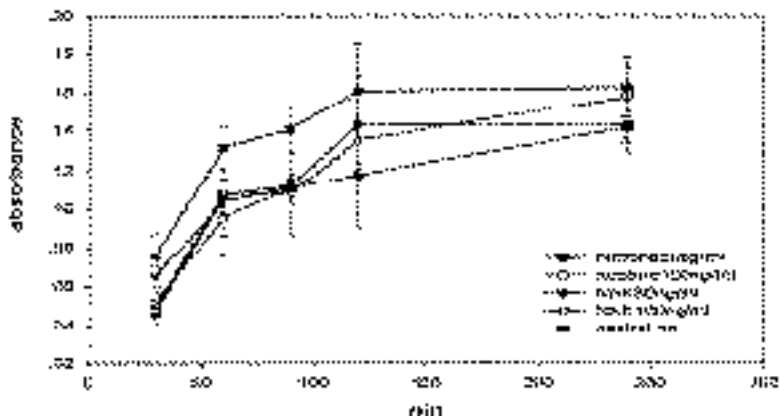


Figure 3. The comparison of non - smoker's gingival fibroblast attachment between treating 50 & 100ng/ml of nicotine and NNK respectively

Table 3. The comparison of non - smoker's gingival fibroblast attachment between treating 50 & 100ng/ml of nicotine and NNK respectively

attachment	non - smoker				
	control	50 ng/ml		100 ng/ml	
		nicotine	NNK	nicotine	NNK
30 min	0.075 ± 0.011	0.045 ± 0.005*	0.064 ± 0.005	0.051 ± 0.005*	0.047 ± 0.003*
60 min	0.131 ± 0.011	0.106 ± 0.008*	0.103 ± 0.017*	0.095 ± 0.019*	0.108 ± 0.007*
90 min	0.140 ± 0.012	0.111 ± 0.003*	0.110 ± 0.005*	0.110 ± 0.007*	0.107 ± 0.020*
120 min	0.160 ± 0.024	0.143 ± 0.025	0.136 ± 0.026	0.117 ± 0.003*	0.135 ± 0.011
240 min	0.162 ± 0.010	0.142 ± 0.013*	0.124 ± 0.005*	0.141 ± 0.008*	0.157 ± 0.020

\*: Statistically significant different from control group(P<0.05)

Figure 4 Table 4  
가

NNK 50,  
Figure 6  
100ng/ml 1  
Table 6

가

3.

NNK

NNK 50, 100ng/ml 3  
Figure 7 Table 7

가

(P<0.05).

NNK 50, 100ng/ml 1  
Figure 5 Table 5

NNK 50, 100ng/ml 3  
Figure 8 Table 8

24 가 (P<0.05).

가

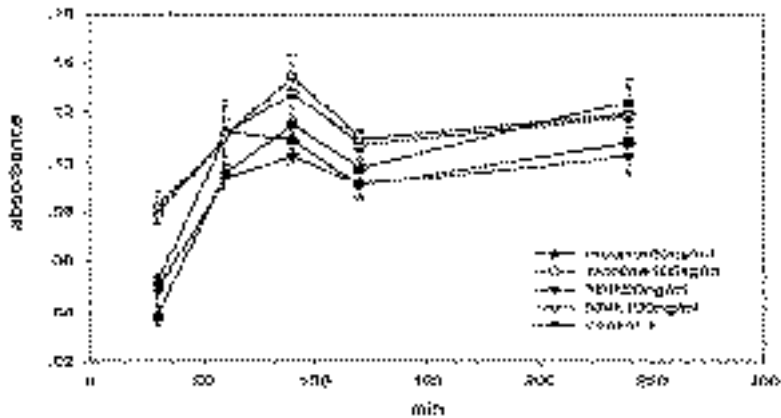


Fig 4. The comparison of smoker's gingival fibroblast attachment between treating 50 & 100ng/ml of nicotine and NNK respectively

Table 4. The comparison of smoker's gingival fibroblast attachment between treating 50 & 100ng/ml of nicotine and NNK respectively

attachment	smoker				
	control	50 ng/ml		100 ng/ml	
		nicotine	NNK	nicotine	NNK
30 min	0.037 ± 0.003	0.050 ± 0.004*	0.047 ± 0.006*	0.078 ± 0.004*	0.081 ± 0.006*
60 min	0.096 ± 0.007	0.111 ± 0.012*	0.094 ± 0.005	0.110 ± 0.011	0.110 ± 0.006*
90 min	0.115 ± 0.011	0.108 ± 0.004	0.103 ± 0.003	0.128 ± 0.004	0.134 ± 0.007*
120 min	0.098 ± 0.008	0.091 ± 0.004	0.091 ± 0.005	0.107 ± 0.004	0.108 ± 0.004*
240 min	0.124 ± 0.007	0.107 ± 0.006*	0.103 ± 0.007*	0.117 ± 0.004	0.118 ± 0.015

\*: Statistically significant different from control group(P<0.05)

1

28).

IV.

가

가

23, 29, 30 - 32).

6

가

7).

26, 27).

(risk marker)

(true risk factor)

5, 6) B - cell T - cell

13,14,21).

51 - 56%

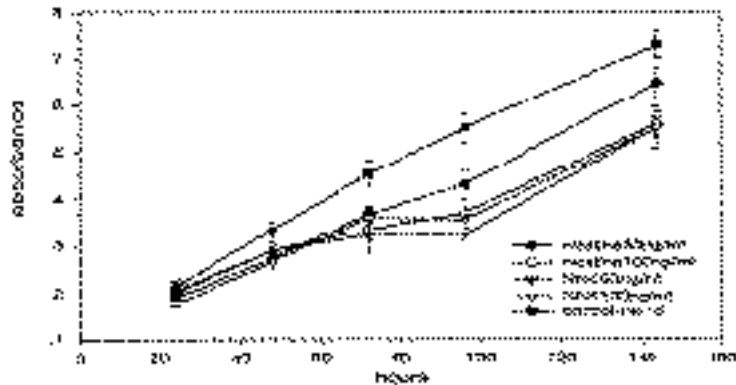


Figure 5. The comparison of non - smoker's gingival fibroblast growth between treating 1 dose of 50 & 100ng/ml of nicotine and NNK respectively

Table 5. The comparison of non - smoker's gingival fibroblast growth between treating 1 dose of 50 & 100ng/ml of nicotine and NNK respectively

1 dose	non - smoker				
	control	50 ng/ml		100 ng/ml	
		nicotine	NNK	nicotine	NNK
24 hr	0.213 ± 0.013	0.190 ± 0.002*	0.200 ± 0.004	0.205 ± 0.003	0.177 ± 0.006*
48 hr	0.332 ± 0.016	0.271 ± 0.004*	0.287 ± 0.016*	0.287 ± 0.016*	0.265 ± 0.017*
72 hr	0.453 ± 0.027	0.366 ± 0.016*	0.322 ± 0.040*	0.335 ± 0.022*	0.360 ± 0.018*
96 hr	0.550 ± 0.029	0.430 ± 0.030*	0.323 ± 0.014*	0.370 ± 0.051*	0.355 ± 0.026*
144 hr	0.728 ± 0.027	0.648 ± 0.033*	0.551 ± 0.023*	0.561 ± 0.024*	0.553 ± 0.042*

\*: Statistically significant different from control group(P<0.05)

7, 8), Macfarlane 33)

15, 36 - 38)

. Kraal beagle

dog

가

39 -

Acitinomyces

41),

sp.

가

가 가

34,

42),

35),

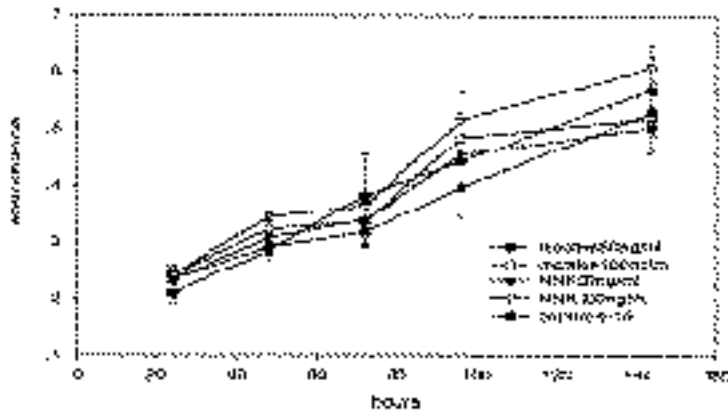


Figure 6. The comparison of smoker's gingival fibroblast growth between treating 1 dose of 50 & 100ng/ml of nicotine and NNK respectively

Table 6. The comparison of smoker's gingival fibroblast growth between treating 1 dose of 50 & 100ng/ml of nicotine and NNK respectively

1 dose	smoker				
	control	50 ng/ml		100 ng/ml	
		nicotine	NNK	nicotine	NNK
24 hr	0.213 ± 0.013	0.210 ± 0.014	0.232 ± 0.006	0.241 ± 0.016	0.242 ± 0.010
48 hr	0.332 ± 0.016	0.284 ± 0.015	0.306 ± 0.004*	0.322 ± 0.009*	0.343 ± 0.008*
72 hr	0.453 ± 0.027	0.381 ± 0.072*	0.336 ± 0.047	0.335 ± 0.037	0.363 ± 0.008*
96 hr	0.555 ± 0.029	0.440 ± 0.037	0.453 ± 0.088	0.483 ± 0.042*	0.513 ± 0.050*
144 hr	0.728 ± 0.027	0.567 ± 0.057	0.501 ± 0.011	0.517 ± 0.062	0.607 ± 0.038*

\*: Statistically significant different from control group(P<0.05)

20 site - of entry  
 carcinogen 48). NNK  
 cytochrome P450  
 43, 44) 49, 50). NNK  
 9) 가 N -  
 45). nitrosornictine(NNN)  
 4 51), NNK  
 , 46), , NNK  
 NNK N - nitrosamines 47) K -  
 ras 10). NNK Mark 2)



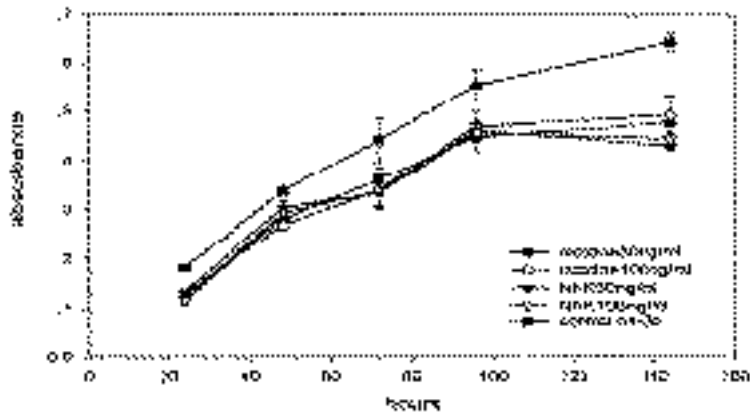


Figure 7. The comparison of non - smoker's gingival fibroblast growth between treating 3 doses of 50 & 100ng/ml of nicotine and NNK respectively

Table 7. The comparison of non - smoker's gingival fibroblast growth between treating 3 doses of 50 & 100ng/ml of nicotine and NNK respectively

3 dose	smoker				
	control	50 ng/ml		100 ng/ml	
		nicotine	NNK	nicotine	NNK
24 hr	0.180 ± 0.006	0.126 ± 0.001*	0.131 ± 0.005*	0.126 ± 0.007*	0.115 ± 0.007*
48 hr	0.336 ± 0.009	0.280 ± 0.017*	0.303 ± 0.012*	0.268 ± 0.010*	0.292 ± 0.008*
72 hr	0.441 ± 0.042	0.361 ± 0.024*	0.331 ± 0.022*	0.338 ± 0.038*	0.337 ± 0.032*
96 hr	0.554 ± 0.029	0.445 ± 0.027*	0.459 ± 0.022*	0.468 ± 0.030*	0.455 ± 0.016*
144 hr	0.640 ± 0.017	0.477 ± 0.054*	0.429 ± 0.009*	0.492 ± 0.039*	0.443 ± 0.012*

\*: Statistically significant different from control group(P<0.05)

(0.025 μM)

, David<sup>3)</sup>  
(0.06mM - 5mM)

NNK

. Figure 1 Table 1

가

fibronectin

. Alpar<sup>4)</sup>

가

0.48mM - 62mM 가

7.8mM

가 50ng/ml

Figure 2, 3 Table 2, 3

52,53)

50, 100ng/ml

NNK

NNK

4 - 5

가

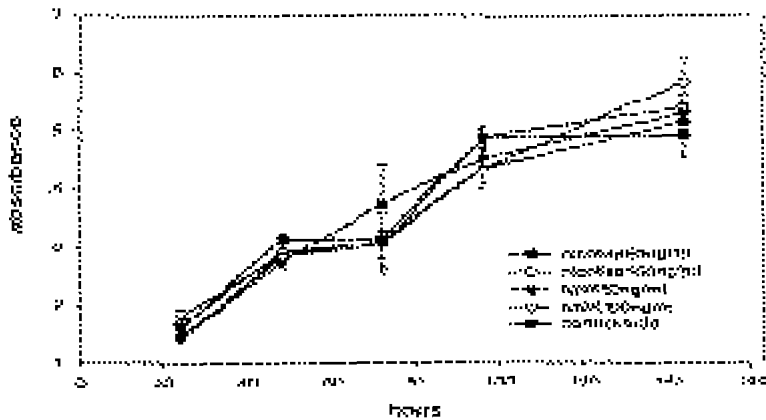


Figure 8. The comparison of smoker's gingival fibroblast growth between treating 3 doses of 50 & 100ng/ml of nicotine and NNK respectively

Table 8. The comparison of smoker's gingival fibroblast growth between treating 3 doses of 50 & 100ng/ml of nicotine and NNK respectively

3 dose	smoker				
	control	50 ng/ml		100 ng/ml	
		nicotine	NNK	nicotine	NNK
24 hr	0.160 ± 0.002	0.143 ± 0.003*	0.140 ± 0.002*	0.165 ± 0.003*	0.180 ± 0.009*
48 hr	0.312 ± 0.009	0.282 ± 0.021*	0.273 ± 0.011*	0.287 ± 0.011*	0.281 ± 0.006*
72 hr	0.315 ± 0.051	0.310 ± 0.057	0.373 ± 0.069	0.307 ± 0.049	0.303 ± 0.023
96 hr	0.488 ± 0.021	0.435 ± 0.035*	0.452 ± 0.013*	0.432 ± 0.026*	0.487 ± 0.014
144 hr	0.492 ± 0.035	0.515 ± 0.013	0.529 ± 0.014	0.584 ± 0.039*	0.539 ± 0.022*

\*: Statistically significant different from control group(P<0.05)

Figure 5, 6, 7, 8      Table 5, 6, 7, 8      NNK      가

Mark<sup>2)</sup>      4 - 5

, NNK

. Mark<sup>2)</sup>

David <sup>3)</sup>

가가 ,  
, 4 - 5

Mark<sup>2)</sup>

(P<0.05).

가

3.

NNK

NNK

NNK가

가

가

가

가

NNK

NNK

NNK

VI.

가

V.

NNK

50, 100ng/ml

30 , 60

, 90 , 120 , 240

24 , 48 ,

72 , 96 , 144

NNK

1 3

1.

(P<0.05).

2.

NNK

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- Abstract -

## The Effect of Nicotine & NNK on Growth & Attachment of Gingival Fibroblast from Smoker and Non-smoker

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Department of Dental Science, The Graduate School, Yonsei University

\*Department of Oral Biology, Dental College, Yonsei University

In order to study the effects of cigarette smoking on periodontal tissue, gingival fibroblast from the smoking and non - smoking groups were cultured and each group were treated with nicotine (50ng/ml, 100ng/ml) and NNK (50ng/ml, 100ng/ml) to test their attachment ability at time intervals of 30minutes, 60minutes, 90minutes, 120minutes, and 240minutes. Using the same method, the growth each group treated with nicotine and NNK in order to compare their attachment ability and growth rate was done.

The Results are as follows.

1. In comparing the attachment ability and growth rate between the smoking and non - smoking group were significantly higher in all time intervals.
2. When the attachment ability was com -

pared among these two groups after treatment with nicotine and NNK, the non - smoking group showed decrease in attachment ability while the smoking group was not affected.

3. The growth rate of these two groups were compared after treating with nicotine and NNK. The growth rate of fibroblast from the non - smoking group decreased while fibroblast from the smoking group was not affected.

These results suggest that fibroblast from the non - smoking group showed higher attachment ability, growth rate, and sensitivity to nicotine and NNK. This implies that fibroblast from the non - smoking group is a more reliable source in testing the cytotoxicity of nicotine and NNK. Also it could be reasonable to think that nicotine and NNK is a probable cause for problems in attachment and repair mechanism.

Key words : nicotine, NNK, gingival

fibroblast, attachment, growth