

수아세포종 세포 배양에서 레티노이드의 세포증식억제 효과

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= Abstract =

The Effect of Retinoids in Medulloblastoma Cell Culture

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The retinoic acid, one of the most popular agents for chemoprevention can inhibit the proliferation of many cancer cells including neuroblastoma and glioblastoma but there is increasing demand reaccessing its in vitro inhibitory effect on the tumor proliferation because of poor responsiveness from recent clinical trial for malignant brain tumor with retinoic acid. It was known to effect on tumor cells by differentiation and apoptosis so that its effect was expected greater in pediatric brain tumor than in adult brain tumor, but there is no report on the effect of retinoic acid in medulloblastoma cell proliferation except all - trans and 13 - cis retinoic acid. Therefore, we compared the effects of all - trans, 13 - cis, and 9 - cis retinoic acid and N - (4 - hydroxyphenyl) retinamide to inhibit proliferation of medulloblastoma tumor cells. Medulloblastoma cells were derived from primary culture of patient's specimen. We estimated the rate of growth inhibition of each tumor cells using MTT assay in the concentration from 10^{-12} M to 10^{-5} M of all - trans, 13 - cis, and 9 - cis retinoic acid and N - (4 - hydroxyphenyl) retinamide. Medulloblastoma cells showed more than 30% growth inhibition by all - trans, 12% by 13 - cis, 20% by 9 - cis retinoic acid and 7% by N - (4 - hydroxyphenyl) retinamide at 14 days culture on the concentration of 10^{-6} M. In conclusion, significantly and dramatic effect by, especially, all - trans retinoic acid, moderate response by 13 - cis retinoic acid and variable or poor response by 9 - cis retinoic acid and N - (4 - hydroxyphenyl) retinamide.

KEY WORDS : All - trans retinoic acid · 13 - cis retinoic acid · 9 - cis retinoic acid · N - (4 - hydroxyphenyl) retinamide · MTT assay · Chemoprevention.

서 론

가
가¹¹⁾⁴⁷⁾⁵²⁾

all - trans, 13 - cis, 9 - cis 가

가

4 - hy -

droxyphenylretinamide(HPR)

all - trans 가 가

¹⁾³⁾²⁵⁾³⁷⁾, 13 - cis 가

³⁴⁾⁵⁴⁾ 가

가

¹⁴⁾²⁰⁾³⁸⁾,

9 - cis 가 가

²⁴⁾

all - trans 13 - cis

가²⁸⁾ growth inhibition) MTT
 가²²⁾ MTT
¹²⁾²¹⁾⁵³⁾ HPR all - trans
 가⁹⁾ 가 가
⁷⁾³²⁾⁴¹⁾ 3
 가³⁰⁾ 1. MTT Assay
 ganglioglioma MTT tetrazolium
²⁰⁾ formazan
 13 - cis 가
¹⁷⁾⁵⁷⁾ all - trans
⁴⁰⁾ try -
 psin (200g, 5)
 10cc 5 × 10⁴
 /ml 9cm petri dish
 pipet 200ul 2 11
 well . 37 , 5% CO₂ 1
 가 3 , 7 , 14
 13 - cis retinoic acid 가 MTT(Sigma, USA) 50 μl(2mg/ml)
³⁶⁾ all - trans 10⁻⁶M well 가 , 37 , 5% CO₂ 4
²⁶⁾ 10⁻⁷M well
 9 - cis 4HPR 가 (60lux)
 . 96 well plate formazan
 . digital multichannel pipette(Ti-
 tertek, Finland)
 가 well . 150 μl dime-
 thyl sulfoxide(DMSO, Sigma, USA) well 가
 (plate shaker) formazan
 36 10 multi - well ELISA auto-
 matic spectrometer recorder(Berhinger ELISA Proce-
 ssor II, Germany) 570nm
 (absorbance, optical density)

연구 범위 및 방법

가⁵⁶⁾
 all - trans, 13 - cis, 9 - cis, 4HPR
 가 GFAP 4 5
 가 all - trans, 13 -
 cis, 9 - cis, 4HPR 10⁻⁶M
 10⁻¹¹M 10⁻⁶, 10⁻⁶, 10⁻⁷, 10⁻⁸, 10⁻⁹, 10⁻¹⁰
 10⁻¹¹M 7 (cell

growth inhibition) MTT
 MTT
 all - trans
 3
 1. MTT Assay
 MTT tetrazolium
 formazan
 try -
 psin (200g, 5)
 10cc 5 × 10⁴
 /ml 9cm petri dish
 pipet 200ul 2 11
 well . 37 , 5% CO₂ 1
 가 3 , 7 , 14
 MTT(Sigma, USA) 50 μl(2mg/ml)
 well 가 , 37 , 5% CO₂ 4
 well
 가 (60lux)
 . 96 well plate formazan
 . digital multichannel pipette(Ti-
 tertek, Finland)
 가 well . 150 μl dime-
 thyl sulfoxide(DMSO, Sigma, USA) well 가
 (plate shaker) formazan
 36 10 multi - well ELISA auto-
 matic spectrometer recorder(Berhinger ELISA Proce-
 ssor II, Germany) 570nm
 (absorbance, optical density)

$$\% = \frac{\text{---}}{\text{---}} \times 100$$

2. Assay for Viability by Dye uptake
 10⁵ 24well culture flask
 2 10% DMEM(Dolbecco's minimal es-
 sential media, Hazleton, USA) . all - trans

가 14 10⁻⁵M 10⁻⁹M 5 RA RA
 가
 trypsin solution 10⁵/ml
 10ul trypan blue 10ul
 trypan blue
 hemocytometer
 % = ————— × 100

결 과

1. MTT Assay

1) All-trans 레티노익 산의 효과

all - trans 4
 10⁻¹²M 113.6 ± 32.1%,
 10⁻¹¹M 116.2 ± 11.9%, 10⁻¹⁰M
 113.0 ± 11.1%, 10⁻⁹M 91.8 ± 14.1%, 10⁻⁸M
 98.6 ± 14.4%, 10⁻⁷M 89.1 ± 13.9%,
 10⁻⁶M 99.5 ± 10.4%, 10⁻⁵M
 84.8 ± 9.8%
 14 10⁻¹²M
 96.2 ± 24.1%, 10⁻¹¹M 97.4 ± 8.5%, 10⁻¹⁰M
 88.4 ± 10.9%, 10⁻⁹M 78.8 ± 14.3%,
 10⁻⁸M 70.2 ± 11.0%, 10⁻⁷M 69.8
 ± 8.9%, 10⁻⁶M 74.4 ± 18.6%, 10⁻⁵M
 38.4 ± 11.1% (Fig. 1).

2) 13-cis 레티노익 산

13 - cis 4

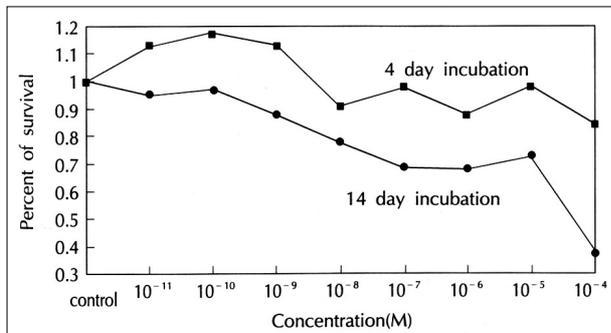


Fig. 1. The result of MTT assay of medulloblastoma cell culture with all-trans retinoic acid shows best response for growth inhibition, which was about 30% on 14th day below 10⁻⁵M.

10⁻¹²M 102.2 ± 10.5%, 10⁻¹¹
 M 94.0 ± 12.4%, 10⁻¹⁰M 99.6 ± 14.0%,
 10⁻⁹M 83.5 ± 3.8%, 10⁻⁸M 79.5
 ± 5.9%, 10⁻⁷M 73.7 ± 6.8%, 10⁻⁶M
 81.5 ± 15.9%, 10⁻⁵M 76.7 ± 17.5%
 , 7
 10⁻¹²M 95.8 ± 24.5%,
 10⁻¹¹M 88.8 ± 8.5%, 10⁻¹⁰M 91.7
 ± 19.2%, 10⁻⁹M 80.7 ± 10.7%, 10⁻⁸M
 72.6 ± 9.3%, 10⁻⁷M 78.0 ± 16.8%, 10⁻⁶M
 85.0 ± 18.0%, 10⁻⁵M 73.1 ±
 12.9% , 14
 10⁻¹²M 119.9 ±
 29.0%, 10⁻¹¹M 103.7 ± 10.0%, 10⁻¹⁰M
 96.1 ± 7.9%, 10⁻⁹M 87.2 ± 4.9%, 10⁻⁸M
 88.0 ± 8.3%, 10⁻⁷M 84.2 ± 4.2%, 10⁻⁶M
 88.0 ± 6.7%, 10⁻⁵M 72.8
 ± 7.4% (Fig. 2).

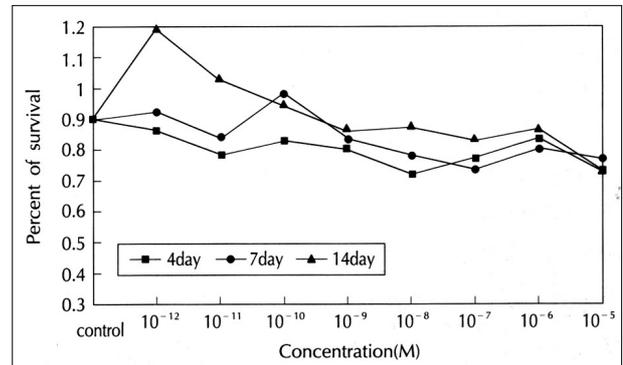


Fig. 2. The result of MTT assay of medulloblastoma cell culture with 13-cis retinoic acid shows moderate response for growth inhibition, which was about 12% on 14th day below 10⁻⁶M.

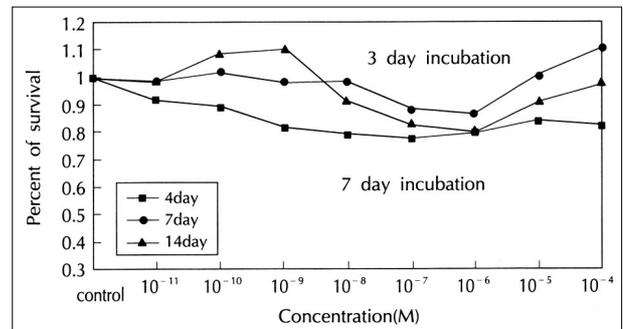


Fig. 3. The result of MTT assay of medulloblastoma cell culture with 9-cis retinoic acid shows variable response for growth inhibition, which was about 20% on 14th day below 10⁻⁵M. However, a significantly variable reverse proliferation was showed in physiologic high concentration of 10⁻⁵M.

3) 9-cis 레티노익 산의 효과

Concentration (M)	4 day	7 day	14 day
Control	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%
10 ⁻¹² M	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%
10 ⁻¹⁰ M	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%
10 ⁻⁸ M	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%
10 ⁻⁶ M	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%
10 ⁻⁵ M	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%
10 ⁻⁴ M	91.2 ± 18.2%	88.7 ± 18.3%	81.1 ± 4.4%

4) 4HPR 레티노익 산의 효과

Concentration (M)	4 day	7 day	14 day
Control	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%
10 ⁻¹² M	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%
10 ⁻¹⁰ M	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%
10 ⁻⁸ M	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%
10 ⁻⁶ M	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%
10 ⁻⁵ M	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%
10 ⁻⁴ M	136.5 ± 66.6%	121.9 ± 17.6%	110.9 ± 15.3%

2. Assay for inhibition of cell growth (Fig. 5)

All-trans

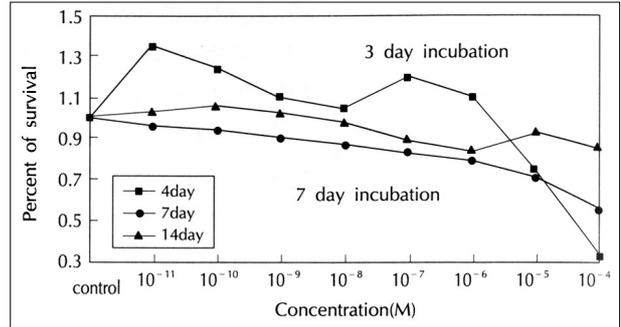


Fig. 4. The result of MTT assay of medulloblastoma cell culture with N-(4-hydroxyphenyl)retinamide shows poor response for growth inhibition, which was about 16% on 14th day below 10⁻⁶M. However, a poor inhibition of growth about 7% in physiologic high concentration of 10⁻⁵M.

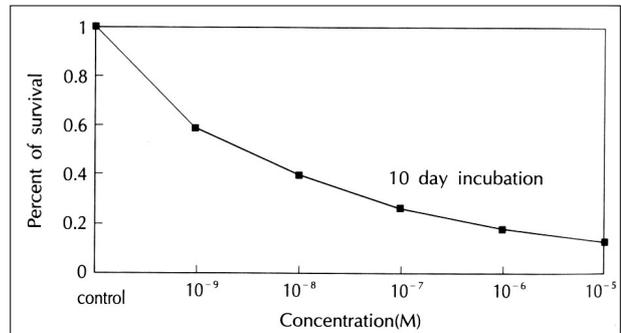


Fig. 5. The result of cell count of medulloblastoma cultured for 14 days with all-trans retinoic acid show dramatic effect in the inhibition of proliferation of medulloblastoma cells.

Concentration (M)	Cell Count
Control	106 ± 12.12 × 10 ⁴ /1.9cm ²
10 ⁻⁹ M	64.3 ± 6.03 × 10 ⁴ /1.9cm ²
10 ⁻⁸ M	39.7 ± 3.51 × 10 ⁴ /1.9cm ²
10 ⁻⁷ M	27.6 ± 3.70 × 10 ⁴ /1.9cm ²
10 ⁻⁶ M	18.7 ± 2.50 × 10 ⁴ /1.9cm ²
10 ⁻⁵ M	13.1 ± 2.50 × 10 ⁴ /1.9cm ²
10 ⁻⁴ M	60.7 ± 9.3%
10 ⁻³ M	37.4 ± 8.9%, 26.0 ± 13.4%, 17.6 ± 13.4%, 12.4 ± 19.1%

고찰

A

(differentiation), (embryogenesis),

29)49) . 1925 Wolbach Howe⁵⁵⁾ 9) ,
A HPR breast cancer cell 가
(metaplasia)가 (class 1 HLA, laminin, 1 integrin chain)
. all - trans 가 , (p185/HER2 on -
가 가 coprotein, EGFR, Mr 67,000 laminin receptor)
가 가 47) 39)가 가
48) .
Retinoic acid isomeric 가
all - trans, 13 - cis, 9 - cis neuroblastoma ,
all - trans 13 - cis 가 가 , 10⁻⁶ 10⁻⁹
가 (1.3) , all - trans M 2)46) .
34)54) , 9 - cis 150mg/m²/day rat C6
가 가 24) t_{1/2} 1.6 1.9 10⁻⁵M
all - trans 53) , HL - 60 5)18) Yung 58) rat C6
all - trans resistant 10⁻⁷ - 10⁻⁶
가 22) . HPR 가 8)20)40)45) .
가 , 35) 가 9 - cis HL - 60
가 가 33) ,
가 가 EGF receptor activity 58) , all - trans 43) Lovat 28) neuroblastoma
. retinoic acid receptor cis 10⁻⁸M 9 - cis all - trans 13 -
(RAR) retinoid X receptor(RXR) , RAR neurite 가 ,
ligand - dependent transcriptional regulator RXR 9 - cis가
heterodimer , RXR ligand - HPR HL60R all - trans
independent auxillary factor 10⁻⁶M 가 HPR 10⁻⁶
50)59) , all - trans RAR RAR M 25% HPR all -
31) 9 - cis RAR RXR trans 9) ,
47) , 13 - cis 6) . cisplatin 0.1uM
. RARb가 50% 0.5uM HPR
19) , cisplatin 0.02uM
RARb 가 , 51) cisplatin
RAR 가 13) , stoma 10⁻⁶M HPR , neurobla -
, RXR agonist LG153 RARb all - trans
RARb RXR 6 2 10 ,
28) . 2 2 , 2
synergy 22) synergy 42) .
27) Neuroblastoma
. RARb RARa¹⁶⁾⁴⁴⁾ g 57) all -
4)15) . HPR trans 13 - cis

수아세포종 세포 배양에서 레티노이드의 세포증식억제 효과

가 10⁻⁶M 83%, MTT
 가 Mork³⁶⁾ 10⁻⁵M 88%가
 가 1 : 1 가
 1uM 13 - cis
 가 , 6
 (neuronal cell marker) (glial all - trans 가 가 , 13 -
 maker) 가 Li - cis , HPR 가 , 9 - cis
 eberman²⁶⁾ 가 D - 283 all - trans 가 Esquenet¹⁰⁾
 10⁻⁶M 10⁻⁷M
 . All -
 trans 13 - cis 9 - cis
 2 4 가
 all - trans 가 가 (p<0.01).
 all - trans MTT
 10⁻⁵M 10⁻⁸M 30%
 4 7 가 가 (p<0.01),
 가 10⁻⁹M 50%
 가 , 10⁻⁶M
 가 , 10⁻⁶M
 all - trans 40%
 , 10⁻⁹M
 가 (Fig. 6).

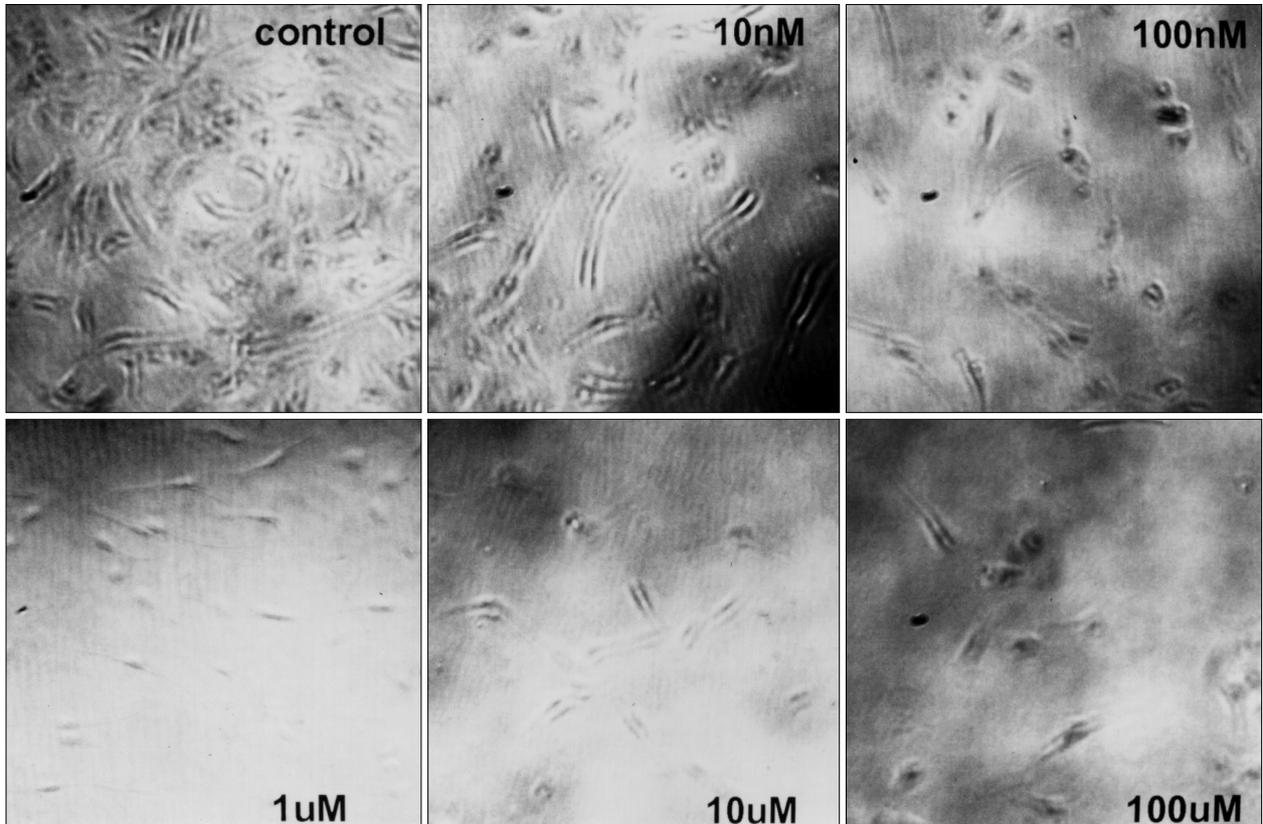


Fig. 6. Medulloblastoma cells cultured for 14days with all-trans retinoic acid of the concentration from 10⁻⁸M to 10⁻⁴M and control group. 10⁻⁵M concentration group of all-trans retinoic acid shows dramatic inhibition upto 90% in the proliferated cell number compared to control group.

	가	all - trans	가
•	: 1998 4 6		
•	: 1998 4 27		
•	:		
	442 - 749		5
	: 0331) 219 - 5664,		: 0331) 219 - 6658

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