

# 알코올리즘의 생물학적 연구와 약물치료\*

## The Biological Research and The Pharmacological Treatment in Alcoholism\*

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### ABSTRACT

In the paper, studies in genetis, reward system, role of neurotransmitters, especially dopamine and opiate system, other biological causes and drug treatments were reviewed. Based on biological hypothesis, various forms of drug treatment have been developed. Treatment for detoxification, for prevention and treatment of withdrawal symptoms, for alcoholism-related mental disorders, for craving and for avoiding drinking behavior were reviewed, too. As biological mechanisms in alcoholism will be clarified in the future, it is expected that new treatment method with specific drugs will be available.

**KEY WORDS :** Biology · Pharmacology · Treatment · Alcoholism.

### 서 론

(alcoholism)

가

가

가 가

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### 생물학적 원인

#### 1. 동물모델

mesolimbic system  
reward durg - seeking behavior  
(preference)  
30  
differential segregation  
(ethanol - preferring, P)  
(ethanol nonpreferring, NP)  
가 Ethanol - preference  
(Walter 1984). 2 3  
(10% v/v) 가  
ad lib  
6 8g/kg ethanol 1 3%  
eth -  
non -  
anol - preferring  
preferring  
가

ethanol - preferring( P) ethanol - nonpreferring( NP)

가

P가

NP P

12

가 P

10 P NP ethanol preference

trait가 , dopamine (reinforcing property) P NP dopamine 가

dopamine D<sub>1</sub> D<sub>2</sub> 가 NP P (Colombo 1995).

P NP가

elevated plus maze open(hostile space) closed(comfortable) open

가

ethanol - naive P 가 NP P NP (Colombo 1995).

14 sP

open

ethanol - experienced NP ethanol - naive NP 가

P ,

가

2. 유 전 가

가 .가 , ,

가

(Goodwin 1979). 가

3 4 . 가 ,

가

가

가 3 4 가

가

(Tarter 1990). Cloninger (1981) 2가 (milieu - limited) 가

가 type 2 (male - limited)

, postnatal environment

CNS , ,

가

Linkage analysis 4, 6 11 gene marker genetic risk (Hill 1975). Restriction Fragment Length

Polymorphism(RFLP)  
 human genome  
 aldehyde dehydrogenase  
 (Yoshida 1984),  
 가  
 가 Blum (1990)  
 Smith (1992) 11 D<sub>2</sub>  
 alcohol - seeking behavior

heterogenous  
 (Plomin  
 1990).  
 Na - K - adenosine triphosphatase  
 가  
 가 (Israel 1965).  
 tetrahydroisoguinoline  
 가 (Myers  
 1989). MAO  
 가  
 Tabakoff (1988) MAO  
 가 adenyI cyclase

3. 신경해부학

opiate, dopamin, serotonin, N - methyl - D -  
 aspartate(NMDA), GABA ventral tegm -  
 ental area(VTA) , nucleus  
 accumbens dopamine  
 . VTA dopamine neuron nucleus accumbens  
 , locus ceruleus (LC)

intracranial  
 self - stimulation(ICSS) VTA dopamine  
 cell  
 GABA VTA LC  
 가  
 cocaine . LC opiate  
 VTA  
 Nasrallah (1983)  
 ( 1990 ; 1993)

가  
 가  
 가  
 가  
 4. 신경전달 물질들  
 가  
 mesolimbic circuitry  
 가  
 가  
 가

5. 알코올의 약리작용

1  
 GABA<sub>A</sub> , NMDA glutamate  
 G -  
 protein, protein kinase, second messenger

ion channel 가 .  
 , ion channel  
 gene tra-  
 nscription protein synthesis , channel,  
 intracellular messenger , synaptogenesis  
 가

LC, mesolimbic dopamine system, ventral  
 tegmental area(VTA) nucleus accumbens  
 (Nestler 1995).

1) Dopamine 체계

dopamine  
 가 (Lippa 1973). dopamine  
 nucleus accumbens  
 hippocampal corna Ammonis 1 cluster  
 dopamine D<sub>2</sub> 가  
 (Liljequist 1978 ; Fadda 1989).

Blum (1990) RFLP  
 dopamine D<sub>2</sub> receptor ass -  
 ociation , 가  
 11 q22 q23  
 Schwab (1991) 가  
 . Smith (1992) D<sub>2</sub> receptor 가

2) Serotonin

Serotonin 가 가  
 5 - HT neurotransmission  
 (Ballenger 1979)  
 5 - HT가 5 - HT

5 - HT agonist  
 (Naranjo 1984), SSRI  
 (Naranjo 1994, 1995ab) 5 - HT 1A  
 partial agonist buspirone, gepirone ipsapirone  
 (Svensson 1993 ; Kra -  
 nzler 1994).

3) Endogenous opioid system

positive reinforcing effect 가

nucleus accumbens endogenous opioids  
 (Wise 1987).

Morphine μ - opioid agonist  
 가 가 (Wild Reid 1990). methadone  
 가 가  
 μ - opioid antagonist  
 (George 1991 ; Vopicelli 1992).  
 가

endorphin .  
 endogenous endorphin (basal defici -  
 ency) . endogenous  
 opiate antagonist  
 가 .  
 가 endorphin release  
 가 가  
 (Gianoulakis de Waele 1994).

4) 수용체

Endogenous receptor  
 가 가 homeostasis

2nd messenger system  
 (gene expression)

6. 기타 연구

1) 알코올중독에 있어 neurosteroid의 역할

steroid  
 steroid neurosteroid  
 neurosteroid Allopregnanolone  
 (ALLO) GABA - - complex  
 GABA  
 (Romeo 1994).  
 benzodiazepine  
 barbiturate  
 GABA<sub>A</sub> positive allosteric modulator

(Liskow Goodwin 1987). GABA down regulation 가

neurosteroid

, GABA<sub>A</sub>

가 (Romeo

1994).

2) 탄수화물대사

carbohydrate - deficient transferrin(CDT)

(Alkenheil 1995). transferrine

. 1976 Stibler가

가 CDT가

CDT가

60gm (alcohol

)

(Stibler 1991). Kabi Pharmacia

CDT 가 20u/l, 26

u/l 60gm

sensitivity 89%

specificity 96% (Ackenheil 1995).

CDT가 marker

(Stible 1993). carbohydrate -

deficient glycoprotein syndrome CDT 가

가

(Jaeken 1991).

3) MAO 활성화도

MAO(monoamine oxidase)

adenyl cyclase activity가

characteristic marker (Tabakoff 1988).

가 가 MAO 가

MAO 가

(Brunner 1993).

4) Evoked potential

Begleiter (1987)

P300 amplituole가

치 료

1. 일반적 원칙

(deto - xification), 2) , 3) ( , ), 4)

1) 알코올제독

가 thiamine

thiamine 100mg

Chlordiazepoxide가

가 diazepam

가 2 1 200mg

25% 가 가

가 lora - zepam

. Diazepam

20mg 1 2

paraldehyde, phenobarbital

phenytoin 가

clonidine, pro -

pranolol

carbamazepine

benzodiazepine

가 가

chlordiazepoxide 4 25mg

chlordiazepoxide 100mg

가

가

2) 유지치료

가  
가  
가가  
가  
Alcoholic Anonymous(AA help group)

3) 약물치료

가  
가  
가  
가  
가 3  
가 50%  
가

2. 술을 빨리 깨게 하는 약물

1) 중추신경 자극제

1960 1970 catecho -  
laminergic agonist(amphetamine, L - dopa, theophyline,  
ephedrine )  
(Alkana  
1977).

naltrexone opiate addiction  
model

가  
가  
ben -  
zodiazepine - GABA - receptor - chloride channel

2) naloxone

1970 narcotic antagonist ,  
naloxone (Jeffcoate 1979).  
(Lyon Antony  
1982), (Bird 1982). Michiels  
(1983) ethanol en -  
dogenous opiate , naloxone

naloxone 가  
(Dole 1982). naloxone  
shock 가 (Peters  
1981). noloxone  
antishock

가 , CNS endorphin enkephalin  
, naloxone  
(Dole 1982).

3) Lithium

Lithium  
(Linnoila  
1974), Lithium “ high ”  
(Judd  
1977).

4) Prostaglandin synthetase inhibitor(ibuprofen)

Minocha (1986) ibuprofen  
visual memory가 ( auditory -  
verbal function ), ibupr -  
ofen 가

3. 금단증상에 대한 약물

1) Benzodiazepine

1965 benzodiazepine  
drug of choice (Mukherjee 1983).



6. 알코올리즘과 관련된 다른 정신과적 장애들에 대한 약물

1) 삼환계 항우울제

가 (O'Sullivan 1984).  
 (Liskow Goodwin  
 1987). TCA 가  
 , alcoholism  
 가  
 가 , 가 , TCA 가  
 가 .  
 가  
 가  
 가 , DST가  
 (Dackis 1984). 2  
 DST가  
 TCA가  
 (Ciraulo 1982).  
 , increasing clearance( 가  
 ) bioavailability가  
 가  
 therapeutic drug monitoring

2) Lithium

lithium  
 가  
 가  
 (Merry 1976)가 . Lithium  
 (Fawcett 1984)  
 lithium  
 가 (Liskow  
 Goodwin 1987).  
 가  
 lithium  
 1981). (Young

3) 항불안제

가 ,  
 가 , 가  
 . benzodiazepine  
 가  
 가  
 buspirone  
 가  
 (Kranzler 1994). serotonin

4) 알코올에 의한 인지장애에 대한 치료

, thiamine  
 (Korsakoff ) 가  
 .  
 . SSRI 가  
 (Weingartner 1983).

7. 갈구를 줄여 음주행동을 약화시키는 약물치료

1) Dopamine 관련 약물

CNS reward pathway dopamine  
 dopamine  
 가 가  
 Tiparide D<sub>2</sub> 가  
 가 neuroleptic effect가

가 (Peters Fa-  
 ulds 1994).  
 Bromocriptine D<sub>2</sub>  
 (Borg 1983).  
 D<sub>2</sub> AI allele 가  
 3 6  
 (Lawford 1995).

2) Serotonin 관련 약물

fenfluramine(Krasner 1976) zimelidine  
 (Naranjo 1984)  
 가 serotonin



ritanserine, fluoxetine citalopram specific serotonin receptor inhibitor(SSRI) (heavy social drinker) (Naranjo 1994, 1995ab). Balldin (1994) citalopram Fluoxetine 가 (Kranzler 1995). 가

17% (Costen McCance - Katz 1995). Ritanserine 5-HT<sub>2</sub> open clinical study ritanserine 14 가

가 (10mg/day) 가 (Naranjo 1995b). Buspirone 5-HT<sub>1A</sub> 가 가 (Kranzler 1994).

3) GABA 관련약물

Acamprosate(calcium acetyl - homotaurinate, C<sub>a</sub> AO - TA) GABA taurine NMDA alcohol - preferring . 3 2 randomized controlled trial acam - prosate placebo 가 (Lhuinter 1990). . 1 randomized controlled trial 가 (Sass 1994).

Gamma - hydroxybutyric acid 3 (Gallimberti 1992). 가 가

가 GABA agonist benzodiazepine . Lhuinter

(1990) acamprosate GABA benzodiazepine 가 benzodiazepine 가 (De - utsch Walton 1977).

4) Endogenous Opioid System opioid system

(rodent, non - human primate) endogenous opioid system alcohol reinforcement , mo - rphine , opiate 가 alcohol - preferring . Opiate 가 . 가

5) Naltrexone

randomized controlled study opiate antagonist naltrexone 1 50mg , 72 exogenous opiate naltrexone 3 placebo (Volpicelli 1992 ; Gianoulakis 1994). naltrexone na - ltrexone placebo ( 5 , 5 가 100mg% ), blood parameter 가 (O' Malley 1992 ; Volpicelli 1992). Naltrexone

naltrexane 가 (high)

(Volpicelli 1992, 1995 ; Swift 1994). Swift (1994) naltrexone

가 , 가 , 가 , 가 .

가 가 naltrexone

- endorphin 가 , 가

endorphin 가 . naltr -

exone - extinction

naltrexone

reward . naltrexone

drink) . (social

naltrexone . nal -

trexone

(가 , , , )

8. 음주를 회피하게 하여 음주행동을 약화시키는 약물

1) Disulfiram

1950 disulfiram

Fuller Roth(1979) disulfiram riboflavin

disulfiram 250mg/d, 1mg/d

8 가 . Disul -

firm 가 가

. 1

가 , 가

가 .

Wilson (1980) disulfiram implant

placebo implant 가

361 307

disulfiram 가 .

Bergstrom (1982) disulfiram implantation

disulfiram - ethanol reaction

disulfiram ,

가 (Azrin

가

1982). disulfiram 가

disulfiram Disulfiram

( , ) , 가

disulfiram dopa -

mine beta hydroxylase , serotonin turnover

biogenic amine biogenic aldehyde

가 . te -

trahydroisoquinoline beta carboline

2) Calcium carbimide

disulfiram aldehyde dehydrogenase 가

24

(disulfiram 6 가 ) , 1

(disulfiram 12 ) . impulsive

drinker dopamine beta de -

hydroxylase . Disulfiram 250mg/d

calcium carbimide 50mg/d

acetaldehyde가 가 , ,

calcium carbimide acetaldehyde

(Peachey 1983). 가

Calcium carbimide 2 가

3) Nitrefazole

Imidazol , trichomonacide

disulfiram 가 aldehyde deh -

ydrogenase 가 3 7

1 가 ,

dopamine beta hydroxylase

calcium carbimide . Nitrefazole - ethanol

4 - methylpyrazole alcohol dehydrogenase inhibitor

acetaldehyde

가 disulfiram - ethanol , carbimide - ethanol

nitrefazole - ethanol

가 .

가 .

결 론

reward system  
opiate

가

중심 단어 :

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