

강박장애의 병태생리와 치료에 있어 세로토닌의 역할*

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Role of Serotonin in Pathophysiology and Treatment of OCD*

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ABSTRACT

The clinical efficacy of serotonin reuptake inhibitors such as clomipramine in the treatment of obsessive compulsive disorder(OCD) has fueled interest in the neurobiological basis of this illness. OCD is responsive exclusively to potent serotonin reuptake inhibitors clomipramine, fluoxetine, fluvoxamine, sertraline, and paroxetine and this point forms the important evidence supporting a central role for serotonin in the pathogenesis of the disorder. Other serotonergic medications such as lithium, buspirone, trazodone, or fenfluramine may be useful as adjuvant treatments in treatment-refractory OCD and adjuvant antipsychotics are useful in tic disorders, personality disorders, and psychotic disorders. This paper reviews results of treatment studies, investigations of biological markers, and neuroendocrine challenges and implications for the role of serotonin in pathophysiology and treatment of OCD.

KEY WORDS : Serotonin · Obsessive-compulsive disorder.

서 론

강박장애(OCD)는 강박관념(obsession)과 강박행위(compulsion)로 구성된다. 강박관념은 반복적이고 불합리한 생각, 이미지, 충동에 의해 특징지어지며, 강박행위는 이러한 생각이나 충동에 의해 유발되는 반복적이고 불합리한 행동이다. 강박장애의 병태생리는 세로토닌의 역할과 관련이 깊다. 세로토닌 재흡수 억제제인 클로미프라민, 플루옥세틴, 플루보キサ민, 세트라린, 파록세틴은 강박장애에 효과적이다. 이는 세로토닌이 강박장애의 병태생리에 중요한 역할을 한다는 증거를 제공한다. 또한 리튬, 부스피론, 트라조돈, 펜플라민은 치료-refractory 강박장애에 보조제로 사용될 수 있다. 항정신병약은 틱장애, 성격장애, 정신병장애에 유용하다. 본 논문은 치료 연구, 생물학적 표지자 연구, 신경내분비학적 도전과제와 세로토닌의 병태생리 및 치료에 대한 역할을 검토한다.

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강박장애의 병태생리

가

(5 - hydroxytryptamine ; 5 - HT) 가 가

(peripheral marker) , (pharm - 1982 ; Flament 1987 ; Thoren 1980b) SRI 5 - HT (Asberg 1982 ; Flament 1987 ; Thoren 1980b) SRI 5 - HT

acological challenge test) 가 가 가 SRI 5 - HT

가 가 .

1. 세로토닌 가설

1) 세로토닌 가설의 근거

(1) 가 (3) (pharmacological challenge test) 가

가 가

clomipramine serotonergic raphe system

가 (Fernandez Lop - prolactin, growth hormone, ACTH

eizbor 1967) , 5 - HT

clomipramine 가

(serotonin reuptake inhibitor : SRI) fluoxetine, fluvox - amine, paroxetine, sertraline 가

(Goodman 1992 ; Greist 1995 ; Jenike 1992).

(, mCPP(meta - chloro - phenyl - piperazine) 5 - HT_{2C}, 5 - HT₃ , 5 - HT_{1A}, 5 - HT_{1D} (Barr 1992), dopamine, acetylcholine, 1 adrenergic, -adrenergic (Hamik Peroutka 1989). Zohar (1987) mCPP 12

가 (Ananth 1981 ; Thoren 1980a ; Zo - olactin cortisol , 가

har Insel 1987).

가 SRI 20 kg 0.5mg pr -

가 가 , 30% . Clomipramine (Clomipramine Collaborative Study Group 1991), SRI 가 . Hollander mCPP

(2) (peripheral marker) 가 Flament 가 prolactin (blunted)가 Charney (1988)

(1987) . mCPP 가 가

clomipramine 가 mCPP (Hollander 1992 ; Zohar 1987) mCPP

가 ,

(Pitman 1989),

약 물 치 료

amphetamine (psychostimulant)
cocaine Tourette's syndrome(TS)

1. 세로토닌 재흡수 억제 약물 : 단독치료(monopharmacotherapy)

clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline

(Von Economo's encephalitis, TS, Sydenham's chorea)

Clomipramine FDA

가 . 가
TS . TS 45 90%
(Swedo 1989 ;
Swedo 1993).
가 . 가 TS
(Leonard 1992),

fluoxetine 20mg, 40mg, 60mg
가 . Wheadon (1993)
348
paroxetine
paroxetine 40mg, 60mg
가 20mg 가
sertraline 가
(Jenike 1990 ; Greist 1995). SRI
clomipramine(1990),
fluoxetine(1995 ; 1994) 가

가
가 . TS "tics of the body"
"tics of the mind" , OCD

fluoxetine 20mg, 40mg, 60mg
가 . Wheadon (1993)
348

SRI 가
SRI
(McDougle 1990).

paroxetine
paroxetine 40mg, 60mg
가 20mg 가
sertraline 가
(Jenike 1990 ; Greist 1995). SRI
clomipramine(1990),
fluoxetine(1995 ; 1994) 가

가 가 가
(McDougle 1990 ; Mcdougle 1991).

SRI buspi-
rone trazodone . Buspi-
rone 가

3. 세로토닌-도파민 상호작용 가설

(TS
가
가
(preclinical study)

(Jenike Baer 1988 ; Pato 1991), trazodone
가
(Pigott 1992b).
가 5-HT NE
venlafaxine 가
(Rauch 1996), duloxetine

tonic inhib-
itory influence 가
, TS
가

mirtazepine .
clomi-
pramine, fluoxetine, fluvoxamine, paroxetine, sertraline 5

가 . 가
가 . Jenike (1990) Greist (1995)
meta - analyses

Table 1. 강박장애의 약물치료 전략

Clomipramine	250mg/day	10
Fluvoxamine	300mg/day	10
Fluoxetine	80mg/day	10
Sertraline	200mg/day	10
Paroxetine	60mg/day	10
SRI		
lithium		
bupirone		
clonazepam		
fenfluramine		
trazodone		
SRI		
SRI	SRI	

(Goodman 1993 ; Jenike Rauch 1994)

ird 1996).

1) 세로토닌 활성도의 강화

30%

가 (La-
SRI ,
가

SRI lithium, bu-
spirone, clonazepam, fenfluramine, trazodone
(Table 1).

SRI 5-HT

5-HT

5-HT

가

SRI L - tryp-
tophan (Ra-
smussen 1984).

impilse
가
가
5-HT 5-HT 가

Bupirone 5-HT_{1a}
nueronal impulse flow
SRI bupirone
가 SRI가

(Jenike 1991 ; Markovitz
1990) fluoxetine bupirone 가
가 (Pigott 1992c ;
McDougle 1993) 가

bupirone
가
SRI
fenfluramine

5-HT 가
fenfluramine 5-HT 가 가 SRI가
가 . Hollander
(1990) 7 7 6 fe-

가 가
Jenike (1990) clomipramine
, clomipramine
가

clomipramine
가
가

30%
40%

가 , 가

2. 병합강화치료(polypharmacotherapeutic augmentation)

가 ,

가
가
가

nfluramine SRI , 5HT 가 SRI , Clonazepam SRI
 가 , ,
 SRI , clonazepam
 , 5-HT₂ 가 가 5-HT
 가 가
 5-HT₂ 가 down - regulation
 trazodone nefa -
 zodone serotonin - 2 antagonist/reuptake inhibitor (SA -
 RI) SARI (Joffe 1996)
 5-HT₂ 5-HT₂
 가 SRI SARI
 가 가
 trazodone SRI
 가 (Lydiard 1986)
 가 (Pigott 1992b)가 SRI
 SRI 5-HT₂
 , SRI SARI
 가 가
 SRI trazodone 가 SRI
 , nefazodone, venlafaxine, rispe -
 ridone 가

3) SRI와 다른 SRI의 병합

3. 새로운 약물

2) 세로토닌 이외의 신경전달물질체계에 작용하는 약물의 병합강화

결론

SRI
 SRI
 SRI 가
 2가 가
 , TS가
 가 SRI 가
 McDougle (1990) fluoxetine 가
 17 가
 9 가 Jacob - SRI
 sen(1995) risperidone 가
 5 3 가
 가 TS
 , schizophreniform - type
 , clonazepam benzodiazepine 가
 중심 단어 :
 참고문헌
 김찬형 · 송동호 · 이홍식 · 최낙경(1995) : 강박장애 환자에서
*Fluoxetine*의 치료효과. 대한정신약물학회지 6(1) : 100-104
 신석철 · 황성근 · 강민희 · 신윤오(1990) : 강박장애 환자에 대

- 한 *Clomipramine Hydrochloride*의 임상효과. *최신의학* 33(5) : 71-77
- 이홍식 · 김찬형 · 송동호(1994) : 강박장애환자에서 세로토닌 효현제인 MK-212가 체온 및 신경내분비 반응에 미치는 효과. *신경정신의학* 33(2) : 420-427
- 이홍식 · 김찬형 · 송동호(1995) : *Fluoxetine* 약물치료를 받은 강박장애환자에서 세로토닌 효현제인 MK-212투여에 따른 체온 및 *Prolactin* 반응의 강화. *신경정신의학* 34(2) : 557-563
- 정희연 · 이병윤 · 임두원 · 권영준(1994) : 강박장애 치료에 대한 *Fluoxetine*의 효과. *대한정신약물학회지* 5 : 77-81
- Altemus MA, Pigott TA, Kalogeras K, Demitrack MA, Dubbert B, Murphy DL, Gold PW(1992) : *Elevations in AVP and CRH in obsessive-compulsive disorder: Pathophysiological implications. Arch Gen Psychiatry* 49(1) : 9-20
- American Psychiatric Association(1994) : *Diagnostic and statistical manual of mental disorders-DSM-IV. 4th ed. Washington DC, American Psychiatric Association*
- Ananth J, Pecknold J, Van den Streen N, Englesmann F(1981) : *Double-blind study of clomipramine and amitriptyline in obsessive neurosis. Progress in Neuropsychopharmacology* 5 : 257-261
- Asberg M, Thoren P, Bertilsson L(1982) : *Clomipramine treatment of obsessive-compulsive disorder : Biochemical and clinical aspects. Psychopharmacol Bull* 18(3) : 13-21
- Barr LC, Goodman WK, Price LH, McDougle CJ, Charney DS(1992) : *The serotonin hypothesis of obsessive-compulsive disorder. Implications of pharmacological challenge studies. J Clin Psychiatry* 4 : 17s-28s
- Bastini B, Nash JF, Meltzer HY(1990) : *Prolactin and cortisol responses to MK-212, a serotonin agonist, in obsessive-compulsive disorder. Arch Gen Psychiatry* 47 : 833-839
- Baxter L(1992) : *Neuroimaging studies of obsessive-compulsive disorder. Psychiatric Clinics of North America* 15(4) : 871-884
- Baxter L, Schwartz J, Bergman K, Szuba M, Guze B, Mazziotta J, Alazraki A, Selin C, Ferny H, Mumford P, Phelps M(1992) : *Caudate glucose metabolic rate changes with both drug and behavior therapy of obsessive-compulsive disorder. Arch Gen Psychiatry* 49 : 681-689
- Charney DS, Goodman WK, Price LH, Woods SW, Rasmussen SA, Heninger GR(1988) : *Serotonin function in obsessive-compulsive disorder : a comparison of the effects of tryptophan and m-chlorophenylpiperazine in patients and healthy subjects. Arch Gen Psychiatry* 45 : 177-185
- Clomipramine Collaborative Study Group(1991) : *Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry* 48 : 730-738
- Dolberg OT, Iancu Y, Sasson Y, Zohar J(1996) : *The pathogenesis and treatment of obsessive-compulsive disorder. Clin Neuropharmacol* 19 : 129-147
- Fernandez CE, Lopez-Ibor JJ(1967) : *Monocloimpramine in the treatment of psychiatric patients resistant to other therapies. Actas Luso Esp Neurol Psiquiatr Cienc* 26 : 119-147
- Flament M, Rapaport J, Murphy D, Lake C, Berg C(1987) : *Biochemical changes during clomipramine treatment of childhood obsessive-compulsive disorder. Arch Gen Psychiatry* 44 : 219-225
- Freeman CPL, Trimble MR, Deakin JFW, Stokes TM, Ashford JJ(1994) : *Fluvoxamine versus clomipramine in the treatment of obsessive-compulsive disorder : A multicenter, randomized, double-blind, parallel group comparison. J Clin Psychiatry* 55 : 301-305
- Goodman W, McDougle C, Price L(1992) : *Pharmacotherapy of obsessive-compulsive disorder. J Clin Psychiatry* 53(4) : 29-37
- Goodman WK, McDougle CJ, Barr LC, Aronson SC, Price LH(1993) : *Biological approaches to treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry* 54(Suppl 6) : 16-26
- Greist J, Jefferson J, Koback K, Katzelnick D, Serlin R(1995) : *Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder : A meta-analysis. Arch Gen Psychiatry* 52 : 53-60
- Hamik A, Peroutka S(1989) : *1-m-Chlorophenyl piperazine (mCPP) interaction with neurotransmitter receptors in human brain. Biol Psychiatry* 25 : 569-575
- Hollander E, DeCaria CM, Gully R, et al(1991) : *Effects of chronic fluoxetine treatment on behavioral and neuroendocrine responses to meta-chloro-phenylpiperazine in obsessive-compulsive disorder. Psychiatr Res* 36 : 161-177
- Hollander E, DeCaria CM, Nitsescu A, et al(1992) : *Serotonergic function in obsessive-compulsive disorder : behavioral and neuroendocrine responses to oral m-chlorophenylpiperazine and fenfluramine in patients and healthy volunteers. Arch Gen Psychiatry* 49 : 21-28
- Hollander E, DeCaria CM, Schneider FR, Schnerder HA, Liebowitz MR, Klein DF(1990) : *Fenfluramine augmentation of serotonin reuptake blockade antiobsessional treatment. J Clin Psychiatry* 51 : 119-123
- Insel T, Mueller E, Alterman I, Linnoila M, Murphy D(1985) : *Obsessive-compulsive disorder and serotonin : Is there a connection? Biol Psychiatry* 20 : 1174-1188
- Jacobsen FM(1995) : *Risperidone in the treatment of affective illness and obsessive-compulsive disorder. J Clin Psychiatry* 56 : 423-429
- Jenike M(1992) : *Pharmacological treatment of obsessive-compulsive disorder. Psychiatric Clinics of North America* 15 : 895-919
- Jenike MA, Baer L(1988) : *Bupirone in obsessive compulsive disorder : An open trial. Am J Psychiatry* 145 : 1285-1286
- Jenike MA, Baer L, Buttolph L(1991) : *Bupirone augmentation of fluoxetine in patients with obsessive compulsive disorder. J Clin Psychiatry* 52 : 13-14
- Jenike MA, Baer L, Summergrad P, Minichiello WE, Hollander A, Seymour R(1990) : *Sertraline in obsessive-compulsive disorder : A double-blind comparison with placebo. Am J Psychiatry* 147 : 923-928
- Jenike MA, Rauch SL(1994) : *Managing the patient with treatment-resistant obsessive compulsive disorder : Current strategies. J Clin Psychiatry* 55(Suppl 3) : 11-17
- Joffe RT, Levitt AJ, Young LT(1996) : *Response to an open trial of a second SSRI in major depression. J Clin Psychiatry* 57 : 114-115
- Koran LM, McElroy SL, Davidson JRT, Rasmussen SA, Hollander E, Jenike MA(1996) : *Fluvoxamine versus clomipramine for obsessive-compulsive disorder : A double-blind comparison.*

- J Clin Psychopharmacol* 16 : 121-129
- Laird LK(1996)** : Issues in the monopharmacotherapy and polypharmacotherapy of obsessive-compulsive disorder. *Psychopharmacol Bull* 32 (4) : 569-578
- Leonard HL, Lenane MC, Swedo SE, Rettew DC, Gershon ES, Rapoport JL(1992)** : Tics and Tourette's disorder. A 2-to 7-year follow-up study of 54 obsessive-compulsive children. *Am J Psychiatry* 149 : 1244-1251
- Lesch KP, Hoh A, Disselkamp-Tietze J, Wiesmann M, Osterheider M, Schulte HM(1991)** : 5-Hydroxytryptamine 1A receptor responsiveness in obsessive-compulsive disorder. Comparison of patients and controls. *Arch Gen Psychiatry* 48 : 540-547
- Lesch KP, Hoh A, Schulte HM, Osterheider M, Muller T(1991)** : Long-term fluoxetine treatment decreases 5-HT1A receptor responsiveness in obsessive-compulsive disorder. *Psychopharmacology* 105 : 415-420
- Lydiard RB(1986)** : Obsessive-compulsive disorder successfully treated with trazodone. *Psychosomatics* 27 : 858-859
- Markovitz PJ, Stagno SJ, Calabrese JR(1990)** : Buspirone augmentation of fluoxetine in obsessive-compulsive disorder. *Am J Psychiatry* 147 : 798-800
- McDougle CJ, Goodman WK, Leckman JF, Holzer JC, Barr LC, McCance-Katz E, Heninger GR, Price LH(1993)** : Limited therapeutic effect of addition of buspirone in fluvoxamine-refractory obsessive-compulsive disorder. *Am J Psychiatry* 150 : 647-649
- McDougle CJ, Price LH, Goodman WK, Charney DS, Heninger GR(1991)** : A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder : Lack of efficacy. *J Clin Psychopharmacol* 11 : 175-184
- McDougle Chj, Goodman WK, Price LH, Delgado PL, Krystal JR, Charney DS, Heninger GR(1990)** : Neuroleptic addition in fluvoxamine refractory obsessive compulsive disorder. *Am J Psychiatry* 147 : 652-654
- Nordahl T, Benkelfat G, Semole W, Gross M, King A, Cohen R (1989)** : Cerebral glucose metabolic rates in obsessive-compulsive disorder. *Neuropsychopharmacology* 2 : 23-28
- Pato MT, Pigott TA, Hill JL, Grover GN, bernstein S, Murphy DL (1991)** : Controlled comparison of buspirone and clomipramine in obsessive-compulsive disorder. *Am J Psychiatry* 148 : 127-129
- Pigott TA, Grady TA, Bernstein SE, et al(1992a)** : A comparison of oral and IV m-CPP in patients with OCD. *Biol Psychiatry* 31 : 173-175
- Pigott TA, Hill JL, Grady TA, et al(1993)** : A comparison of the behavioral effects of oral versus intravenous mCPP administration in OCD patients and the effects of metergoline prior to i.v. mCPP. *Biol Psychiatry* 33 : 3-14
- Pigott TA, L'Heureux F, Hill JL, Bihari K, Bernstein SE, Murphy DL(1992c)** : A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol* 12 : 11-18
- Pigott TA, L'Heureux F, Rubenstein CS, Bernstein SE, Hill JL, Murphy DL(1992b)** : A double-blind, placebo-controlled study of trazodone in patients with obsessive-compulsive disorder. *J Clin Psychopharmacol* 12 : 156-162
- Pigott TA, Pato MT, Bernstein SE, Grover GN, Hill JL, Tolliver TJ, Murphy DL(1990)** : Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive compulsive disorder. *Arch Gen Psychiatry* 47 : 926-932
- Pigott TA, Zohar J, Hill JL, et al(1991)** : Metergoline blocks the behavioral and neuroendocrine effects of orally administered m-chlorophenylpiperazine in patients with obsessive-compulsive disorder. *Biol Psychiatry* 29 : 418-426
- Pitman RK(1989)** : Animal models for compulsive behavior. *Biol Psychiatry* 26 : 189-198
- Rasmussen SA(1984)** : Lithium and tryptophan augmentation in clomipramine-resistant obsessive-compulsive disorder. *Am J Psychiatry* 141 : 1283-1285
- Rauch SL, O'Sullivan RL, Jenike MA(1996)** : Open treatment of obsessive-compulsive disorder with venlafaxine : A series of ten cases. *J Clin Psychopharmacol* 16 : 81-84
- Rolls E, Williams G(1987)** : Sensory and movement-related neuronal activity in different regions of the primate striatum. In : *Basal ganglia and behavior: Sensory aspects of motor functioning*, Ed by Schneider JS, Lidsky TI, Toronto, Saunders
- Salzman L, Thaler FH(1981)** : Obsessive-compulsive disorder : a review of the literature. *Am J Psychiatry* 138 : 286-296
- Stahl S(1988)** : Basal ganglia neuropharmacology and obsessive-compulsive disorder : The obsessive-compulsive disorder hypothesis of basal ganglion dysfunction. *Psychopharmacol Bull* 24 (3) : 370-374
- Swedo SE, Leonard H, Shapiro MB, Casey BJ, Mannheim GB, Lenane M, Rettew DC(1993)** : Sydenham's chorea : Physical and psychological symptoms of Saint Vitus dance. *Pediatrics* 91 : 706-713
- Swedo SE, Rapoport JL, Cheslow DL, Leonard HL, Ayoub EM, Hosier DM, Wald ER(1989)** : High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am J Psychiatry* 146 : 246-249
- Thoren P, Asberg M, Bertelsson L, Mellstrom B, Sjoqvist F, Traskman L(1980b)** : Clomipramine treatment of obsessive-compulsive disorder, II : Biochemical aspects. *Arch Gen Psychiatry* 37 : 1289-1294
- Thoren P, Asberg M, Crohnholm B, Jornestedt L, Trachman L (1980a)** : Clomipramine treatment of obsessive-compulsive disorder. I. A controlled clinical trial. *Arch Gen Psychiatry* 37 : 1281-1285
- Tollefson GD, Rampey AH, Potvin JH, Jenike MA, Rush AJ, Dominguez RA, Koran LM, Shear MK, Goodman W, Genduso LA(1994)** : A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 51 : 559-567
- Wheadon DE, Bushnell WD, Steiner M(1993)** : A fixed-dose comparison of 20, 40, 60mg paroxetine to placebo in the treatment of obsessive compulsive disorder. Presented at the annual meeting of the American College of Neuropsychopharmacology, Honolulu, December 13-17
- Zohar J, Insel T(1987)** : Obsessive-compulsive disorder : Psychobiological approaches to diagnosis, treatment, and pathophysiology.

Biol Psychiatry 22 : 667-687

Zohar J, Insel TR, Zohar-Kadouch RC, Hill JL, Murphy DL (1988) : Serotonergic responsivity in obsessive-compulsive disorder : effects of chronic clomipramine treatment. *Arch Gen Psy-*

chiatry 45 : 167-172

Zohar J, Zohar-Kadouch RC, Kindler S(1992) : Current concepts in the pharmacological treatment of obsessive-compulsive disorder. *Drugs* 2 : 210-218