

내측 전전두피질에 6-hydroxydopamine 주입 후 흰쥐 신선조체 도파민 수용체의 변화에 관한 자가방사기록법적 연구

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An Autoradiographic Study on the Rat Neostriatal Dopamine Receptor Changes after 6-hydroxydopamine Injection into the Medial Prefrontal Cortex

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국문초록

(prefrontal cortex) 가 6-hydroxydopamine 2 D₁ D₂ 가
 6-hydroxydopamine 2 D₁ Bmax (p<0.01). 6-hydroxydopamine D₂ Bmax Kd regulation) 가 D₁ (up
 중심 단어 : 6-hydroxydopamine.

서 론

가 ,¹⁾²⁾
 가 가
 (synapse) (release) 가
 (hypersensitivity)
 가
 가 (mesocortical) (me-

: 1995 11 15
 : 1999 2 9

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solimbic) 가 가
³⁾ , 가가
, . Weinberg²¹⁾ 가
D₂ , 가
(corticostri-
4-6) . atal glutaminergic pathway) 가
, 가가 ,
7)8) . 가 (mesolimbic system) 가
, 가 가가 가 . 가
9-11) 가 ,
¹¹⁾ , (working memory)
(PET) ²²⁾
가가 ,
가 가
, ,
(prefrontal cortex)
(hypofrontality),¹³⁻¹⁵⁾ ,²³⁻²⁶⁾ [³H] - spiperone
, ,²⁶⁾ tyrosine hy-
¹⁶⁾ droxlyase²⁷⁾ 가가 .
, ,
¹⁷⁾¹⁸⁾ D₁ D₂
, 가 가
(Wisconsin Card Sort) (stereotaxic sur-
, gery)
6 - hydroxydopamine(6 - OHDA)
가 ,¹⁹⁾
Okubo ²⁰⁾ PET , - (caudateputamen)
D₁ (nucleus accumbens)
가 ,
D₁ D₂ 가
가 , (autoradiography) .

연구대상 및 방법

1. 실험동물 및 재료

(20 22), 12 (7)
 250 350g Sprague - Dawley
 6 - OHDA Sigma
 D₁ [³H]SCH
 23390(spec. act. 73.2Ci/mmol), D₂
 [³H]Spiperone(spec. act. 21.3Ci/mmol) New
 England Nuclear 가
 (autoradiography) Hyperfilm - ³H
 Amersham

2. 입체외과수술(Stereotaxic surgery)

30
 6 - OHDA desipra -
 mine 25mg/kg chloral
 hydrate 380mg/kg atropine
 sulfate 0.2cc(0.5mg/cc)
 15

1.5mm
 glass pippete(tip 60 80um) rat brain atlas
 28) (bregma 3.5ml
 , 0.7ml , dura 3.5ml
 ; AP +3.5 from bregma ; ML ±0.7 from
 midline ; VD 3.5 from dura)

6 - OHDA(8ug/1.5 µl/min) 1
 2 3 glass pippete

penicilline G procaine suspension 75,000 U

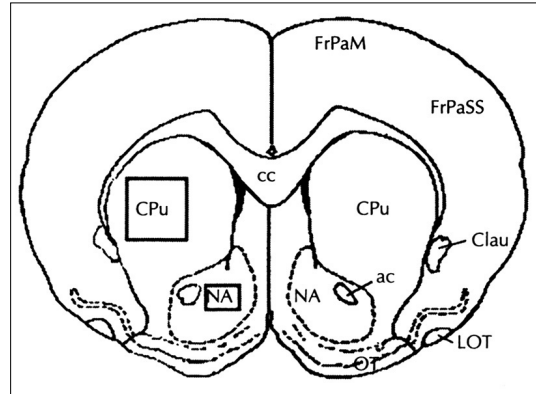


Fig. 1. Cursor box placements in brain regions of coronal sections collected 9.2 to 10.2mm anterior to the interaural plane are represented here at anterior. Left hemisphere labels apply to neuro-anatomical names according to Paxinos and Watson(1986). ac, anterior commissure ; cc, corpus callosum ; Clau, claustrum ; CPu, caudate-putamen ; FrPaM, frontal parietal motor cortex ; FrPaSS, frontal parietal somatosensory cortex ; LOT, lateral olfactory tract ; NA, nucleus accumbens ; OT, olfactory tubercle.

2
 sham lesion saline 1.5 µl

3. 조직 준비 및 보온(Incubation)

6 - OHDA 2
 (decapitation) ,
 (cracking)
 - 40 isopentane
 - 70
 interaural line 9.2
 10.2mm cryostat(- 14) 20 µm
 coronal section 가
 interaural line 9.2 10.2mm
 (corpus
 callosum), (anterior commissure)
 (lateral ventricle) interaural line 9.2mm
 48 gelatin
 (thawmounted) slide box
 - 20 2 5
 . Gelatin 1L

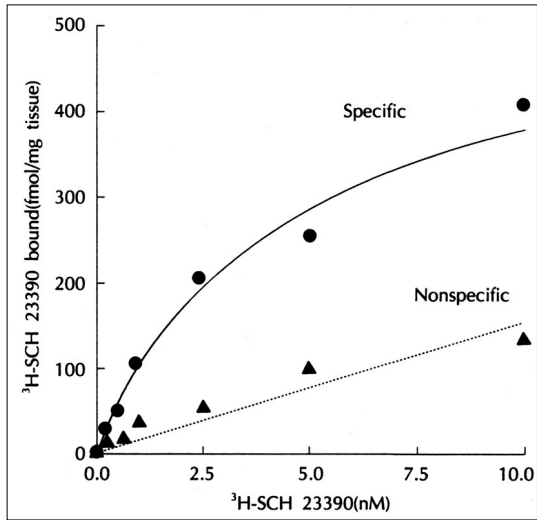


Fig. 2. Saturation curve for $^3\text{H-SCH 23390}$ binding (D_1 receptor binding) in caudate-putamen sections of rat. Specific and non-specific binding of $^3\text{H-SCH 23390}$ to striatal sections.

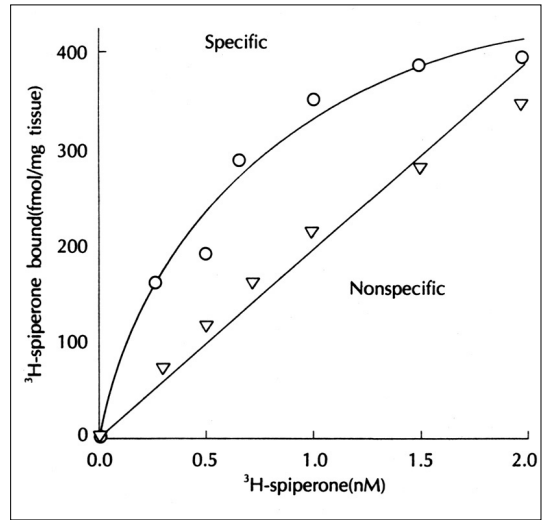


Fig. 4. Saturation curve for $^3\text{H-spiperone}$ binding (D_2 receptor binding) in caudate-putamen sections of rat. Specific and non-specific binding of $^3\text{H-spiperone}$ to striatal sections.

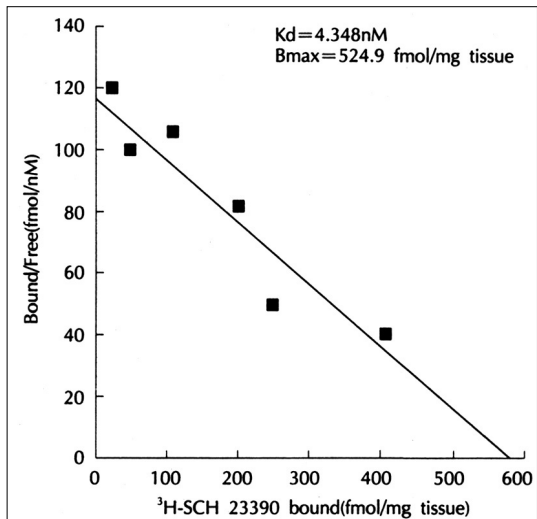


Fig. 3. Representative scatchard plot of specific $^3\text{H-SCH 23390}$ binding (D_1 receptor binding) in caudate-putamen sections of rat.

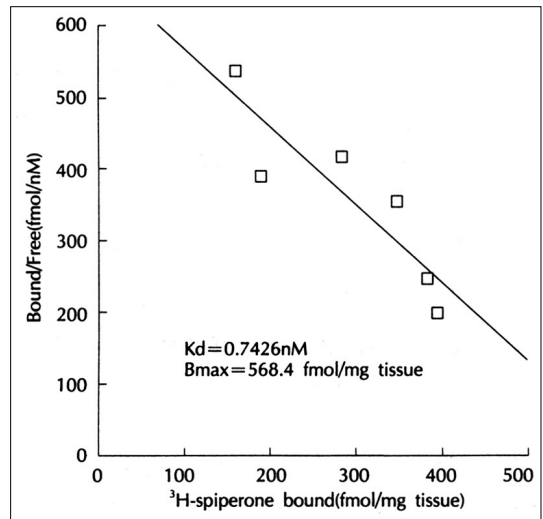


Fig. 5. Representative scatchard plot of specific $^3\text{H-spiperone}$ binding (D_2 receptor binding) in caudate-putamen sections of rat.

gelatin 4gm 60 가 가
 0.8gm chromium potassium
 sulfate Whatman No. 1 filter paper
 30
 - 20
 120mM NaCl, 20mM CaCl₂, 5mM KCl, 1mM

MgCl₂, 0.01% ascorbic acid, 1 μM pargiline
 20mM Tris - HCl buffer (pH 7.4) 0 5
 (preincubation) 90
 . D₁ [³H]SCH 23390
 0.2, 0.5, 1.0, 2.5, 5.0, 10.0nM 6가
 , 5 - HT₂ 1
 mianserin 20nM . ice

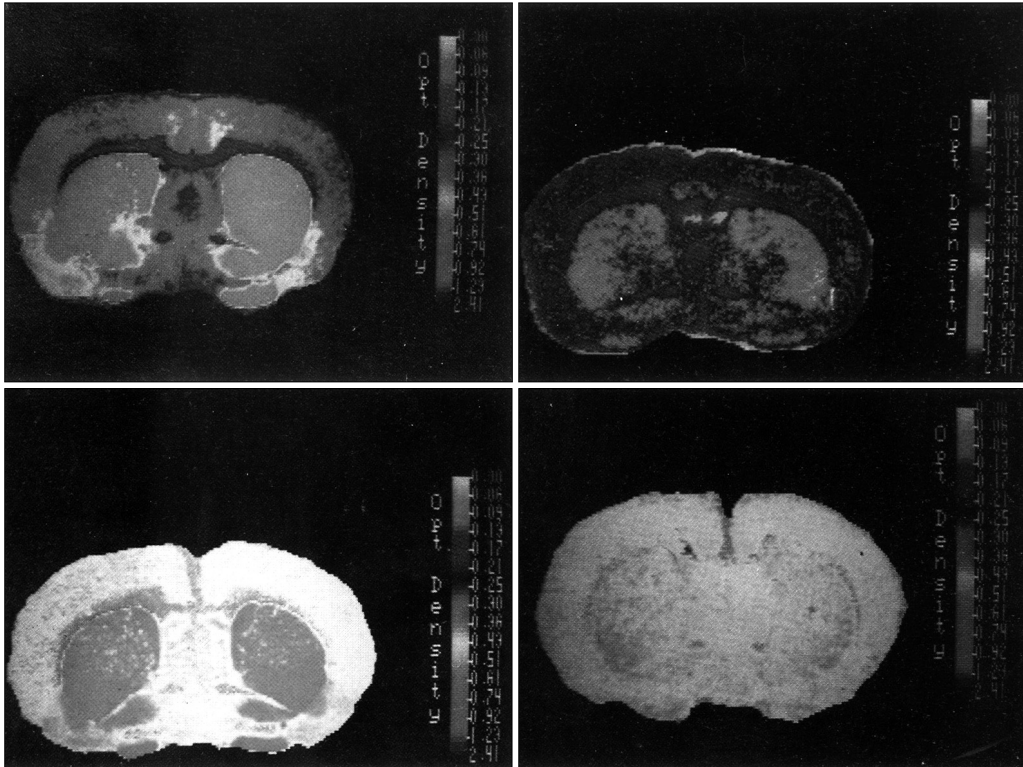


Fig. 6. Autoradiographic distribution of [³H]SCH 23390 binding in caudate-putamen and nucleus accumbens. Illustrated are a 6-hydroxydopamine injected rat (upper part) and a shamlesioned rat (lower part). Total binding (left side) and nonspecific binding (right part) are shown.

cold buffer 5 0
 10 μM butaclamol
 D₂ [³H]spiperone
 0.3, 0.5, 0.7, 1.0, 1.5, 2.0nM 6가
 5-HT₂ 1
 mianserin 100nM
 ice cold buffer 5 0
 butaclamol 2 μM

4. 자기방사기록법 및 컴퓨터 영상분석

X-ray
 cassette Hyperfilm - ³H 3 ([³H]SCH23390),
 fmol/mg tissue weight 4 ([³H]spiperone) Kodak D19 3
 [³H] - microscale(Amersham) 1 Kodak

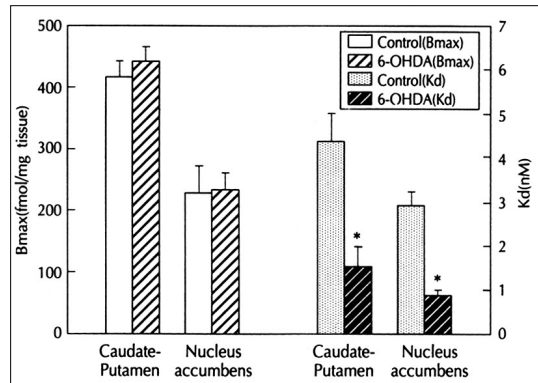


Fig. 7. Comparison of Bmax and Kd of D₁ receptor in caudate-putamen and nucleus accumbens between control and 6-OHDA group. *p<0.05, as compared with control group (by Mann-Whitney U-test)

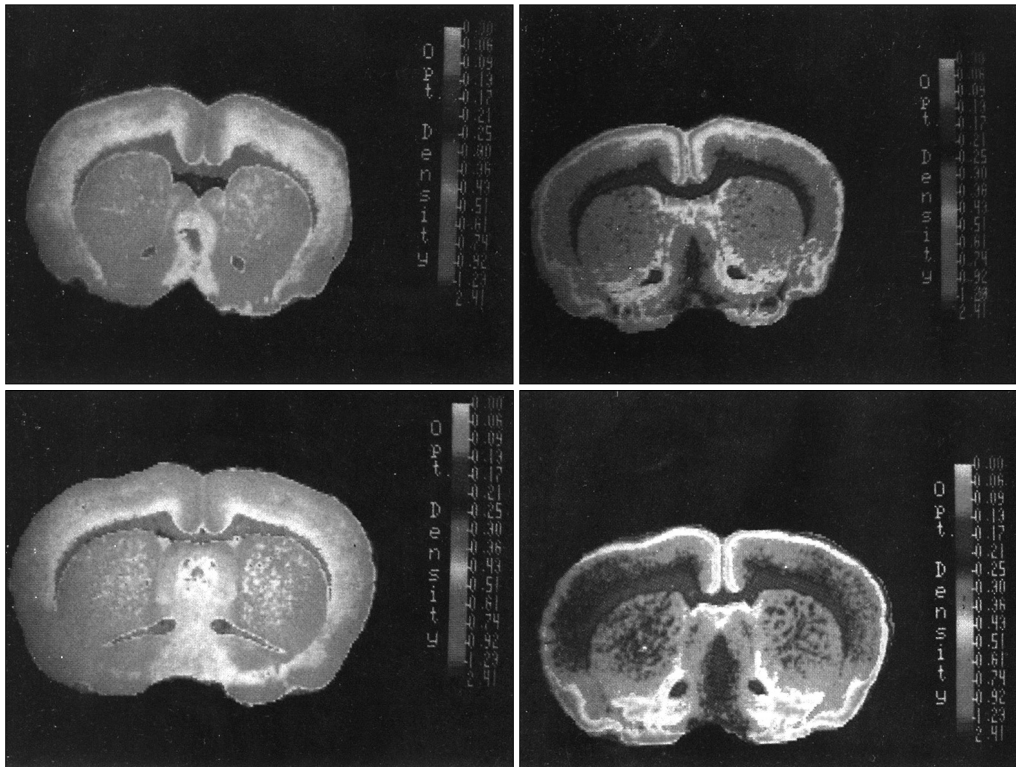


Fig. 8. Autoradiographic distribution of [³H]spiperone binding in caudate-putamen and nucleus accumbens. Illustrated are a 6-hydroxydopamine injected rat(upper part) and a sham-lesioned rat(lower part). Total binding(left side) and nonspecific binding(right part) are shown.

rapid fixer 4

digital autoradiographic system Amersham RAS - R1000 receptor analysis system . Video camera(Dage - MTI series 68 NEWVICON)

color TV monitor 2 for D₁ ; 4 for D₂ , Scat - chard (maximum number of binding site) B_{max} (dissociation constant) K_d (3 for D₁ ; 5 for D₂).

(calibration) microscale (optical density)

(area of interest) (mouse)

. D₁

D₂

(1)

Paxinos Watson Atlas(1986)

fmol/mg tissue weight (2 for D₁ ; 4 for D₂) , Scat - chard (maximum number of binding site) B_{max} (dissociation constant) K_d (3 for D₁ ; 5 for D₂).

5. 통계처리

6 - OHDA

SPSS

Bmax Kd (version 7.01) Mann - Whitney test

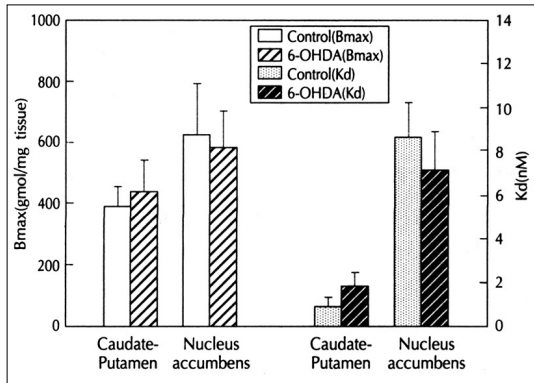


Fig. 9. Comparison of Bmax and Kd of D₂ receptor in caudate-putamen and nucleus accumbens between control and 6-OHDA group.

Bmax 583.44 ± 123.55fmol/mg tissue
 615.09 ± 178.57fmol/mg tissue
 가 , Kd
 7.43 ± 1.60nM 8.84 ± 1.36nM
 가 (9).
 고 찰
 (ventral tegmental area
 (A10)) (A9)
 가

결 과

1. 내측 전전두엽(MPF)에 6-OHDA 투여후 흰쥐 뇌의 D₁ 수용체의 변화

6 - OHDA (N=10)
 (N=7) D₁ 가 (6).
 D₁ Bmax 443.24 ± 42.10fmol/mg tissue
 가 , Kd 420.16 ± 23.13fmol/mg tissue
 1.52 ± 0.30nM 4.37 ± 0.65nM
 (p<0.01).

Bmax 232.27 ± 22.91fmol/mg tissue
 227.63 ± 22.50fmol/mg tissue
 가 , Kd 0.86 ± 0.10nM,
 2.91 ± 0.45nM
 (p<0.01)(7).

2. 내측 전전두엽(MPF)에 6-OHDA 투여후 흰쥐 뇌의 D₂ 수용체의 변화

6 - hydroxydopamine (N=9) (N=8) D₂ 가 (8).
 D₂ Bmax 445.20 ± 76.87fmol/mg tissue
 ± 67.78fmol/mg tissue 가 390.35
 가 , Kd 1.88 ± 0.45nM,
 0.93 ± 0.31nM 가 .

(23)(25)(26)(29)
 2 D₁
 (up - regulation) , D₂
 가 D₁
 가 (affi -
 nity) 가 .
 가 (presynaptic)
 30)
 . Leccese
 Lyness²³⁾ 6 - OHDA 10
 DOPAC HVA 가가
 , - 가
 , Martin - Iverson²⁴⁾ 6 - OHDA
 12 -
 DOPAC/DA , DA 가
 . Pycock²⁶⁾ 6 -
 OHDA 7
 (DA) HVA 가
 , 1 DA HVA 가 [3H]spi -
 perone,[3H]ADTN 가 .
 가

가
 ,
 가⁴³⁾
 6 - OHDA
 D₁
 D₂ 가
 D₁ D₂
 DA 가³¹⁾
 가³²⁻³⁷⁾
 ,
 가
 가⁴⁹⁾ D₁
 adenylate cyclase가⁵⁰⁾가
 D₁ SCH23390
 D₂ 가⁵¹⁾ SCH23390
 가 D₂ agonist
 가³⁸⁻⁴⁰⁾
 가⁴¹⁻⁴³⁾ Young Bradford⁴⁴⁾
 (hemidecortication)
 가⁵²⁾
 (autoradiography)
 (Quantitative receptor autoradiography :
 QAR) 가
 D₁
 Robert Anderson⁴⁵⁾ I -
 D₂ 가
 glutamate 가⁵³⁾
 ,⁵⁴⁻⁵⁶⁾ D₁ QAR
 glutamate 가⁵⁷⁾ QAR
 ,
⁴⁶⁻⁴⁸⁾ Carter (1988) glutamate가
 Bmax
 가⁵⁸⁾
 kainate 가 NMDA
 가 (autoradiography)
 NMDA
 atropine
 ,
 ibotenate
 NMDA가

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- 가
 NMDA ibotenic
 acid 가

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ABSTRACT

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The frontal cortex of rat is innervated by dopaminergic pathway (mesocortical pathway) arising from ventral tegmental area. Several studies have suggested that mesocortical dopaminergic neurons may modulate the function of dopaminergic neurons at subcortical sites. The effect of lesions of the dopaminergic nerve terminals in the medial prefrontal cortex of the rat on dopamine D_1 and D_2 receptors within the striatum and olfactory tubercle has been investigated. Bilateral 6-hydroxydopamine lesions were stereotaxically placed in the medial prefrontal cortex. Animal were pretreated with desipramine to block the uptake of neurotoxin into noradrenergic terminals and to make it more selective for dopamine terminal. After 2 weeks later, we examined the changes of D_1 and D_2 receptors in caudate-putamen and nucleus accumbens by quantitative autoradiography using the specific D_1 antagonist [^3H]SCH23390 and D_2 antagonist [^3H]spiperone.

The results shows that D_1 receptor at striatum was up regulated 2 weeks after destruction of dopamine terminals within medial prefrontal vortex of the rat. This findings suggest that frontal cortical dopamine system may regulate the dopamine system in corpus striatum.

KEY WORDS : Prefrontal cortex · Striatum D_1 and D_2 Receptors · 6-hydroxydopamine.