

비전형적 항정신병약물에 의한 체중증가의 기전 및 약리유전학

이 준 노*[†] · 양 병 환**

The Mechanisms of Atypical Antipsychotics-Induced Weight Gain and Related Pharmacogenetics

Joon-Noh Lee, M.D., *[†] Byung-Hwan Yang, M.D. ****ABSTRACT**

The use of atypical antipsychotics is limited by occurrence of adverse reactions such as weight gain, despite of their benefits. This article provides a comprehensive review and discussion of the most significant findings regarding obesity - related pathways and integrates these with the known mechanism of atypical antipsychotic action. The focus of this article is primarily on the genetics of obesity related pathways that may be disrupted by atypical antipsychotics. This review also discussed weight gain, hyperglycemia or occurrence of diabetes while being treated with atypical antipsychotics from the point of view of pharmacogenetics. Pharmacogenetic research seeks to uncover genetic factors that will help clinicians identify the best treatment strategies for their patients. It will aid clinically in the prediction of response and side effects, such as antipsychotic - induced weight gain, and minimize the current "trial and error" approach to prescribing in the near future.

This article also presents the genetics of both central and peripheral pathways putatively involved in antipsychotic - induced weight gain while providing a comprehensive review of the obesity literature. This article also review obesity related candidate molecules which may be disrupted during atypical antipsychotic drug treatment.

KEY WORDS : Atypical antipsychotics · Weight gain · Phrmacogenetics.

서 론

Seoul National Hospital, Seoul, Korea

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Department of Neuropsychiatry, College of Medicine & the Mental, Health Research Institute, Hanyang University, Seoul, Korea

[†]교신저자 : , 143 - 711 3) (02) 2204 - 0178,) (02) 458 - 0731 E - mail) jn1879@hanafos.com

(preadipocyte)가 가 ,
 가 . Peroxisome proli-
 ferator - activated receptor(PPAR)가

()
 가 ()

1. 시상하부(Hypothalamus)

가 ,
 , 가
 , 가
 “ ”
 3

가
 , 가
 , 가
 leptin (catabolic pathway) NPY
 (anabolic pathway)

2. Leptin과 Insulin

Leptin insulin
 .⁵⁾ Leptin
 (obesity gene, ob) ,
 . Lepin

(lateral hypothalamic area)
 가 melanin - concentra-
 ting hormone(MCH), orexins neuropep-
 tide Y(NPY) (NPY1, NPY5)
 (arcuate nucleus, ARC) -
 (blood - brain - barrier, BBB)
 , NPY, agouti - related protein(AGRP) pro -
 opiomelanocortin(POMC)
 (paraventricular nucleus, PVN) ARC
 가
 orexins, pro - opiomelanocortin(PO-
 MC), galanin, - melanocyte stimulin hormone(-
 MSH), NPY(Y1, Y5)
 (ventromedial nucleus, VMN)
 (dorsomedial nucleus, DMN) leptin

variant) ‘ long form ’ leptin (ObRb
 , ,
 (cascades) . ObRb
 ARC, VMN DMN
⁶⁾ Lep-
 tin
 CNS
 . leptin
 가 BMI (positively
 correlated) .⁷⁾ Leptin
⁷⁾⁸⁾ Leptin
⁹⁾ Lep-

⁵⁾
 가
 (catabolic)

Zhang ¹⁰⁾ mouse ob
 . (ob/ob
 mouse) . ob/ob mice
 leptin
 가
⁷⁾¹¹⁾ ‘ short form ’ leptin

(Ob/Ra variant) BBB leptin ³⁰⁾ insulin NPY ARC
leptin mouse ¹⁴⁾¹⁵⁾ fa/fa rat ¹⁶⁾ leptin ¹²⁾¹³⁾ db/db NPY mRNA 가 ³¹⁾³²⁾
leptin 가 leptin 가
Clozapine olanzapine ¹⁷⁾¹⁸⁾ leptin 가
leptin 가 가
가
leptin leptin ¹⁹⁾ (orexigenic molecule) Y1 Y5
leptin 가
Insulin pancreatic - cell leptin ³⁴⁾ 가 가 , hyperinsulinemia, hypertriglyceridemia, insulin 가가
가 ²⁰⁾ ³⁴⁾ ³⁵⁾
BBB NPY
⁵⁾ insulin 가 ARC leptin insulin 가
CNS 가
DMN insulin 가 ARC ⁵⁾²¹⁾ leptin insulin 가 , ARC neuron NPY
specific insulin receptor가 mice(NIRKO mice) ²²⁾ in- leptin insulin ARC
sulin ²³⁾ Insulin ³⁶⁾ PVN, DMN, VMN NPY 가 가
insulin ²⁴⁾ VMN ²⁵⁾ insulin 가 ³⁷⁾
²⁶⁾ Wood ⁶⁾ leptin insulin NPY 가 가
insulin 가 glucocorticoid ³⁴⁾³⁹⁾
가 NPY 가
, NPY Y1 Y5 ⁴⁰⁾⁴¹⁾
leptin ²⁷⁾ insulin ²⁸⁾ Clozapine insulin NPY (complex nature) 가
olanzapine 가 ¹⁸⁾²⁹⁾
insulin NPY

NPY (가),⁴²⁾⁴³⁾ (가),
),
 4. 그 외 체중조절에 관련된 중추 및 말초적 신호들
 Leptin insulin ARC NPY
 가
 ARC POMC 가 . PO-
 MC - MSH가 leptin
 . - MSH melanocortin
 , MC3R MC4R
 . MC4R
 leptin
 , leptin mela-
 nocortin . MC3R/
 MC4R agouti - related protein(AGRP) ARC
 NPY POMC/ - MSH
 가 가
 .⁴⁴⁾ , POMC/ - MSH
 NPY/agouti - related protein(AGRP)
 .
 가
 , orexins/
 hypocretins, galanin, MCH ,
 cocaine and amphetamine - regulated transcript(CA-
 RT) corticotropin - releasing factor(CRF)
 가 .

**비전형적 항정신병약물에 의한 체중증가와
 당뇨병유발 및 악리유전학적 고찰**

1. 체중증가

가 ,
 . Allison ²⁾ 81
 3 10
 . molindone 0.39kg
 .⁵²⁾⁵³⁾

thioridazine 3.19kg 가
 , 가 clozapine 4.45kg,
 olanzapine 4.15kg, sertindole 2.92kg, risperidone
 2.10kg ziprasidone 0.04kg 가 . Wirshing
⁴⁵⁾ . Wetterling⁴⁶⁾
 2000 3 Medline
 가
 olanzapine(2.3kg/month), clozapine(1.7kg/month),
 quetiapine(1.8kg/month), zotepine(2.3kg/month)
 가 , risperidone(1.0kg/month), zipra-
 sidone(0.8kg/month) . 가 12
 가 가
 clozapine olanzapine . Hong ⁴⁷⁾ 4
 clozapine 2.4kg 가
 가 - 17.5kg 12.9kg
 . Umbricht ⁴⁸⁾ 82 clozapine
 6~12 가가
 , 20% 가
 50%
 . Henderson ³⁵⁾ clozapine
 5 46 가가
 . Kinon ⁴⁹⁾ 573 olanzapine
 3 가가 39
 (plateau) 6.26kg
 가 가 ,
 BMI가 가 .
 Nemeroff⁵⁰⁾ olanzapine
 가 ,
 가 가 1
 5~20mg/day
 가가

clozapine
 가 ,
 . clozapine 가
⁴⁸⁾⁵¹⁾
 .⁵²⁾⁵³⁾

70% 가

phenothiazine 2 (57/58) 56)

2. 당뇨병유발

phenothiazine 2 (57/58) 56)

clozapine 10% (oral glucose tolerance test) Hagg 64)

12% 가 2 (glucose intolerance) Henderson 35)

30 (36.6%) 5 82

gaga 가

29)65)

clozapine 2

gaga 가

risperidone 2 quetiapine

2~20% 66)67)

clozapine, 68-70) olanzapine 65)71)72)

risperidone 73)74) quetiapine 75)

gaga , 가 ,

insulin (glucose tolerance)

Insulin 2

insulin 가

Insulin insulin

insulin - sensitive glucose transporters (GLUT) microsome GLUT 59)60)

insulin 가 2 (translocation) 61)

insulin 가 2

5-HT_{1A} (pharmacogenetics)

30)

가 insulin 가

62)63)

3. 체중증가에 대한 약리유전학적 연구

가 , 가 가 . ,

가 10 .

clozapine 가 , ,

⁷⁶⁾⁷⁷⁾ 가 (false - positive)

가 , 가

가 , 가

“ complex trait ” ⁷⁸⁾ 가 “ (population stratification) ”

가 가

가 (measures) , BMI, waist - to - hip , (, HDL, LDL, triglyceride), leptin, insulin pro-lactin

가 , 가

가 , 가 (signal - to - noise ratio)

⁴⁹⁾⁷⁹⁾ 가 가

가 가 (penetrance)

가 가

200 가 가 ,

가 ⁸⁰⁾⁸¹⁾ 가 가

가 (linkage 가가

study) 가 40 가 ⁸²⁾

가

가

(association study)

2 (ph-

TNF - lin ¹²³⁾¹²⁴⁾ insu-
 가 3 ¹²⁵⁾
 uncoupling protein 3
 (UCP1 - 3) / 64 tryptophan
 UCP1 arginine (Trp64Arg)가 insulin
 BAT ¹¹³⁾ UCP2 ¹¹⁴⁾ ¹²⁶⁾ 2 ¹²⁷⁾
 WAT ¹¹⁵⁾
 UCP3 ¹¹⁶⁾ BAT 가 ¹²⁸⁾ Hinney ¹¹⁹⁾
 UCPs
 ATP (oxidative phosphorylation) (uncoupling) , Fogelholm ¹²⁹⁾ 3
 가 Trp64Arg UCP - 1 A -
 가 ¹¹⁷⁾ >G 가 12
 UCP 가 가 40
 가가 , UCP 가 가
 UCP 가 가
 3 1 Leptin 가
 WAT, BAT, ¹¹⁸⁾ POMC (- MSH, - en-
 1 WAT, BAT PVN leptin epinephrine 1 ¹³⁰⁾ BBB
 protein kinase A ¹¹⁹⁾ 3 ¹³¹⁾
 perilipin (麻黃) ephedrine ,
 lipase 가 가 3
 UCPs protein . Clozapine
 kinase A가 CREB (transcription factor) 3 1
 UCP 가 . 1 가 ¹⁷⁾ ,
 IP3, DAG가 가 UCP 가
¹¹⁷⁾
 3
 가 2 가 40~50% muscarin 가 , clozapine
 insulin 10~100 가 ¹²⁰⁾¹²¹⁾ 3 ¹³²⁾ Yamada
 insulin , trigly-
 ceride 가 가 ¹²²⁾ 3 가
 , 3
¹²¹⁾ 3 leptin/melanocortin
 UCP1 - 3 가 . 3 system (downstream) MCH system
 (upstream)

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