

우울증의 새로운 신경생물학*

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The New Neurobiology of Depression*

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ABSTRACT

Recent basic and clinical studies demonstrate a major role for neural plasticity in the etiology and treatment of depression and stress-related illness. The neural plasticity is reflected both in the birth of new cell in the adult brain (neurogenesis) and the death of genetically healthy cells (apoptosis) in the response to the individual's interaction with the environment. The neural plasticity includes adaptations of intracellular signal transduction pathway and gene expression, as well as alterations in neuronal morphology and cell survival. At the cellular level, repeated stress causes shortening and debranching of dendrite in the CA3 region of hippocampus and suppress neurogenesis of dentate gyrus granule neurons. At the molecular level, both form of structural remodeling appear to be mediated by glucocorticoid hormone working in concert with glutamate and N-methyl-D-aspartate (NMDA) receptor, along with transmitters such as serotonin and GABA-benzodiazepine system. In addition, the decreased expression and reduced level of brain-derived neurotrophic factor (BDNF) could contribute the atrophy and decreased function of stress-vulnerable hippocampal neurons. It is also suggested that atrophy and death of neurons in the hippocampus, as well as prefrontal cortex and possibly other regions, could contribute to the pathophysiology of depression. Antidepressant treatment could oppose these adverse cellular effects, which may be regarded as a loss of neural plasticity, by blocking or reversing the atrophy of hippocampal neurons and by increasing cell survival and function via up-regulation of cyclic adenosine monophosphate response element-binding proteins (CREB) and BDNF. In this article, the molecular and cellular mechanisms that underlie stress, depression, and action of antidepressant are precisely discussed.

KEY WORDS : Neural plasticity · Intracellular signal transduction · Apoptosis · Neurogenesis · Stress · Depression.

서론

1950

가 re-

serpine 15%

reserpine 가

가

가

가 (Schildkraut 1965).

가 (serotonin ; 5-HT)

(norepinephrine ; NE)

2001
"Recent advances in understanding of depression"

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가 , 가 5-HT NE 가 가 5-HT_{2A} 가 (Butler 1993). , 5-HT_{1A} 가 Blier deMontigny(1994) . 가 somatodendritic 5-HT_{1A} 가 가 presynaptic 5-HT_{1A} . 가 , SSRIs 5-HT presynaptic 5-HT_{1A} (adaptive desensitization) 5-HT 가 . 가 dorsal raphe 5-HT_{1A} , 5-HT 가 (Blier de Montigny 1998). 5-HT_{1A} pindolol SSRIs (Zanardi 1997 ; Bordet 1998)가 . , (Berman 1997 ; Perez 1999) pindolol pindolol 가 (monoamine receptor sensitivity hypothesis) (Sulser 1978 ; Charney 1981). 가 가 가 (down - regulation) (up - regulation) 가 (-adrenergic receptor ; AR) (Vetulani Sulser 1975 ; Banerjee 1977). , 5-HT_{2A} (Peroutka Snyder 1980). 가 가 , 가 AR 5-HT_{2A} (Heninger Charney 1987). 가 , AR 5-HT_{2A} (Riva Creese 1989). , cyclic adenosine monophosphate(cAMP) AR AR 가 neurotrophic factor 가 . 가 , (Pay- (cerebral cortex), (amelkel 1982 ; Avorn 1986). , AR 가 ygdala) 가 (O Donnell 1993), (neuroanatomical circuit)가 AR 가 (Goodwin 1982). ,

가
가 . 가
가 , ,
.

신경가소성(Neural Plasticity)

가 (neural plasticity) 가 (structural plasticity)

가 (neuronal adaptation)
(neurogenesis)
(apoptosis)

neurotrophic factor

가 ,
[cyclic adenosine monophosphate response element - binding protein(CREB)].
(convergent factor)

(CREB BDNF)

(Duman 2000)(1).

1. 세포내 신호전달 경로(Intracellular signal transduction cascade)

가 neurotrophic factor
가 가

(cAMP) cyclic adenosine monophosphate neurotrophic factor 가

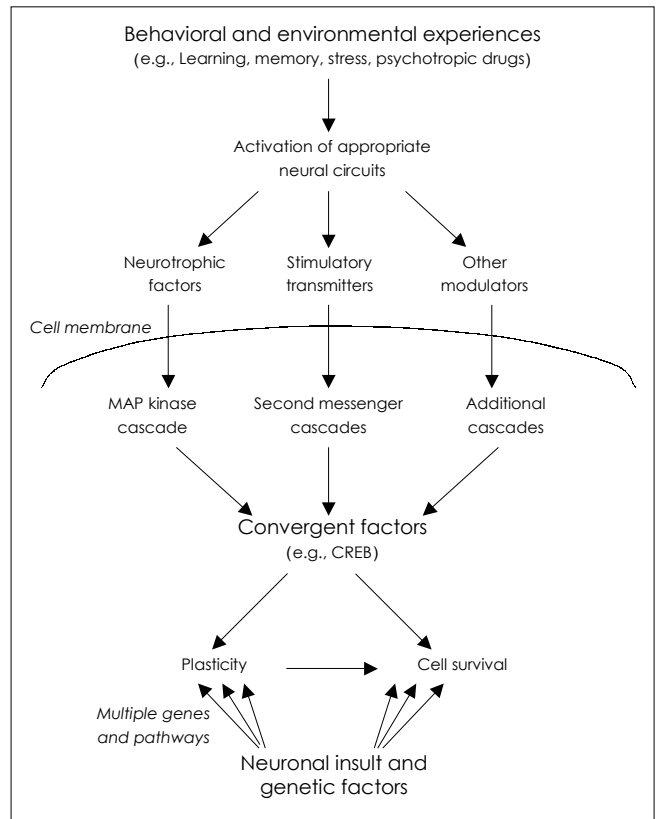


Fig. 1. Model for interaction of neural plasticity and cell death pathways.

1) 세포내 cAMP 신호전달경로

cAMP

AR 5-HT_{4,5A,6,7}
cAMP , 5-HT_{1A,1B,1D,1E}
G
adenylyl cyclase(AC) , AC adenosine triphosphate(ATP) cAMP 가 , cAMP
cAMP - dependent protein kinase(PKA)
PKA , (ion channel), G , ,
(transcriptional factor)
cAMP
cAMP responsive element, CRE) , cAMP
CREB(cAMP response element binding protein)
, CREB cAMP - dependent protein kinase(PKA) 가 . CREB
. CREB
Ser 133 가 . CREB
protein kinase C(PKC)
Ca²⁺/calmodulin(CAM) - dependent protein kinase

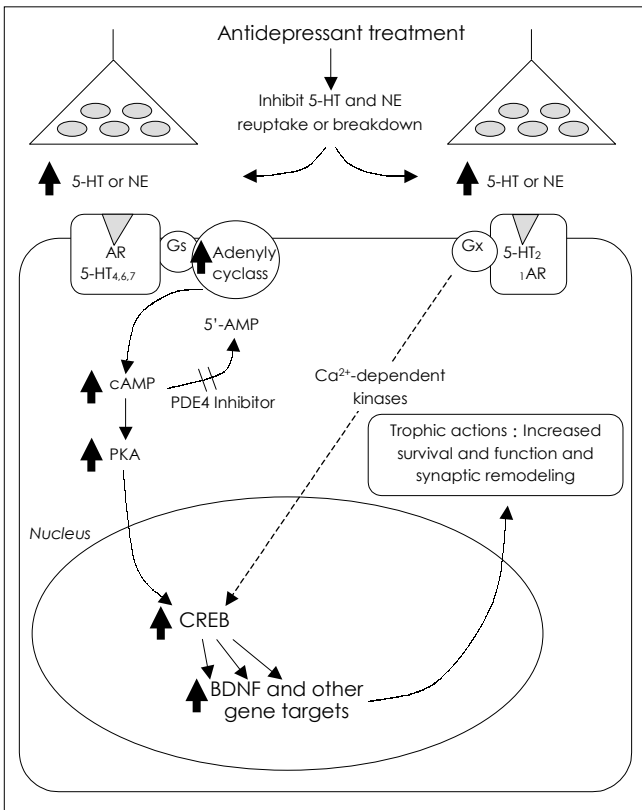


Fig. 2. A model of the action of antidepressant treatment on cAMP signal transduction cascade.

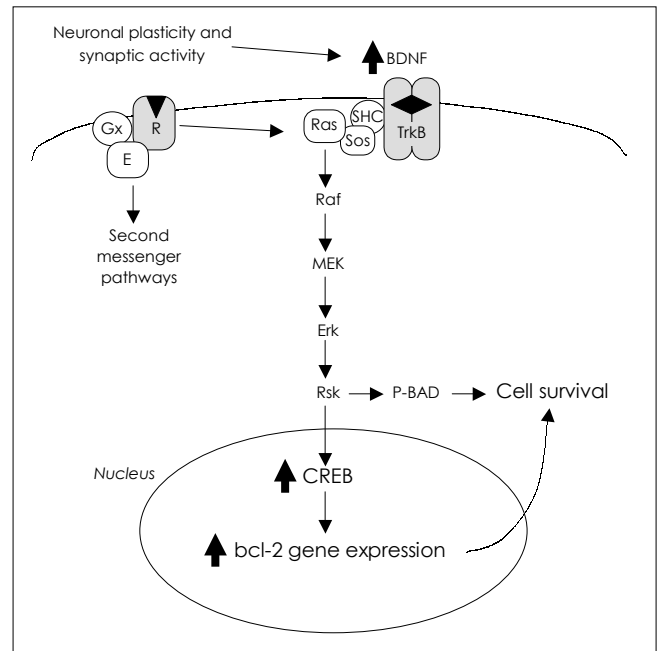


Fig. 3. Model of the neurotrophic factor-mitogen-activated protein (MAP) kinase cascade and regulation of cell survival.

. 가 , HT_{2A} phosphatidylinositol inositol triphosphate(IP3) diacylglycerol(DAG) Ca²⁺ PKC CAM kinase . CREB BDNF(brain - derived neurotrophic factor) TrkB(transmembrane receptor protein tyrosine kinase B) (target gene)

(target neuron) 가 가 (Duman 1999)(2).

2) Neurotrophic factor 신호전달경로

Neurotrophic factor 가 (Russell 1995)(3). Neurotrophic factor Trks(transmembrane receptor protein tyrosine kinase) , (nerve growth factor) TrkA, BDNF TrkB, Neurotrophin(NT) - 3/NT - 4/5 TrkC . BDNF TrkB (Shc, Sos, Ras, Raf, MEK) MAP kinase (ErK) . Trk phosph-

olipase C phosphatidylinositol - 3 - kinase 가 . MAP kinase 가 ribosome S6 kinase(Rsk) , Rsk 가 (Bonni 1999). , Rsk

pro - apoptotic factor BAD . Rsk CREB anti - apoptotic factor Bcl - 2 . Bcl - 2 (promoter) CREB가 CRE 가 (Finkbeiner 2000). MAP kinase (AR) G (internalization) cAMP (Luttrell 1999)

(4). AR soluble tyrosine kinase(Src) , Src adaptor protein Shc, Gab Ras MAP kinase가 . AR - arrestin - arrestin G (desensitization) . - arrestin AR Src adaptor 가 . cAMP - CREB MAP kinase . 5 - HT_{1A} (Mendez 1999). G cAMP 5 - HT_{1A} 가 cAMP

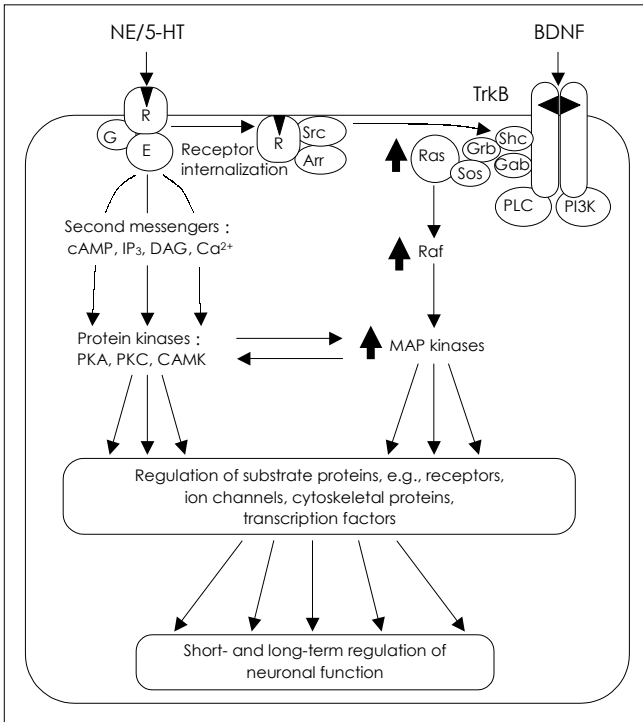


Fig. 4. A model demonstrating the signal transduction pathways for neurotrophic factor.

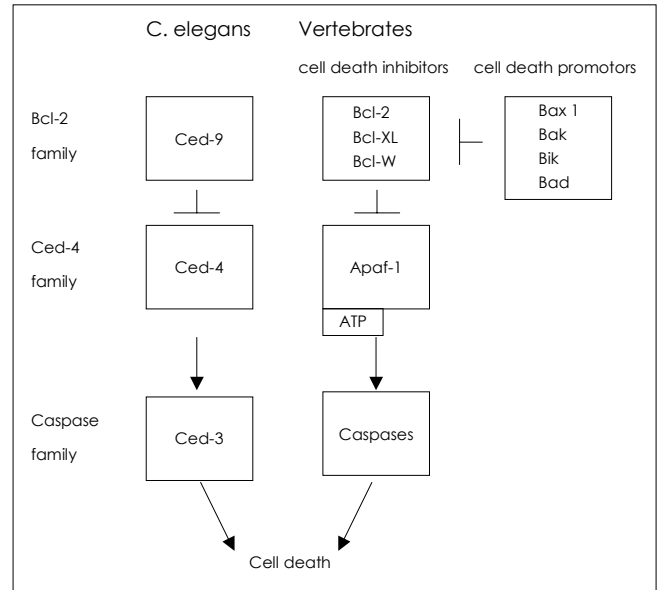


Fig. 5. A genetic pathway for cell death in worms and vertebrates.

MAP kinase

2. 아포프토시스(Apoptosis)

가 (suicide program) 가 (programmed cell death). (necrosis)가 (acute traumatic injury) (lysis) (accidental death) (shrinkage), (chromatin) (condensation), (cellular fragmentation), (phagocytosis) (natural death) 1980 T 가 (survival signal) 가 (Wyllie 1987). 가 RNA

Bcl - 2 가 (Caenorhabditis elegans) Ced - 3, Ced - 4 (cell death gene) , Ced - 9 (Kendel 2000)(5). Apaf - 1(apoptosis activating factor - 1) caspases(cysteine protease family) , Bcl - 2 family Bcl - 2, Bcl - XL, Bcl - W (cell death inhibitor) , Bax 1, Bak, Bik, Bad (cell death promotor) , neurotrophic factor (nerve growth factor) trk A Bcl - 2 Apaf - 1 caspase Apaf - 1 BDNF 가 (Stahl 2000) , 가 (Eilat 1999) 가 (Lucassen 2001) 가

스트레스와 신경가소성

1. 해 마

(temporal lobe)
 entorhinal cortex (axon)
 (dentate gyrus) (granular neuron)
 mossy 가 CA3 (pyramidal
 neuron), CA3 CA1
 trisynaptic circuit
 (Sapolsky 2000)(6).

(short - term memory)
 (long - term explicit memory)
 (consolidation) , - -
 (feedback) (Eichenbaum Ott 1992).
 type (mineralocorticoid) type (glu-
 cocorticoid) 가
 (DeKloet 1998).
 (gonadal hormone) ,
 5 - HT_{1A} 가
 5 - HT_{1A}

CA3 (dendrite) (shortening)
 가 (debranching) , (dendritic
 remodeling) (McEwen 1999),

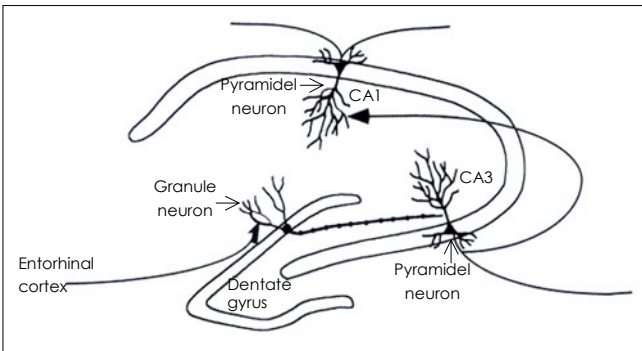


Fig. 6. Hippocampal trisynaptic circuit.

(dentate gyrus) (granule neuron)
 가 , , (neurogenesis)
 (Gould Tanapat 1999).

2. 스트레스에 의한 수상돌기 개조

(dendritic remodeling) CA3
 (apical dendrite)
 (atrophy) 가
 가 CA3 (pyramidal neuron)
 (adrenal glucocorticoid)
 (McEwen 1999).
 CA3 3가
 (Duman 1999), ,
 CA3 (atrophy)
 ,
 CA3 (death)
 ,
 CA3 (neuroendanger-
 ment). (Sousa 2000) CA3
 CA1 가

3. 스트레스에 의한 신경조직발생 억제

가
 (dentate gyrus)
 (neurogenesis)
 (granular neuron)
 (Eriksson 1998 ; Greenough 1999).
 가 (enri-
 ched - environment living),
 (Kempermann 1997 ; van Praag 1999).
 (Gould 1999).
 (Gould 1998). (adrenalectomy)
 가
 (Cameron McKay 1999).

가 가 (Moghaddam 1994), mossy fiber terminal(MFT) 가 (Chittajallu 1996). 가 (vesicle) 가 (Magarinos 1997) 가 (reorganization) 가 (Cameron 1998). NMDA NMDA (cyto-skeleton) 5-HT_{1A} 5-HT_{1A} (transporter) 5-HT (Mckitrick 2000), 가 5-HT_{1A} 5-HT_{1A} mRNA (Lopez 1999 ; Maines 1999), 5-HT_{1A} (Lopez 1998) 5-HT_{1A} 가 가 5-HT_{1A} 가 (co-localization) 5-HT NMDA 5-HT2 (Rahmann Neumann 1993). tianeptine (Watanabe 1992a). GABA - benzodiazepine CA3 가 CA3 (interneuron) mossy CA3 (Freund Buzsaki 1996), CA3 entorhinal cortex (excita-

4. 수상돌기 개조와 신경조직발생의 분자적 기전

가 가 가, NMDA , GABA (7). Entorhinal cortex NMDA 가 NMDA NR2A NR2B mRNA 가 (Weiland 1997), CA3 GABA_A (Orchinik 1994),

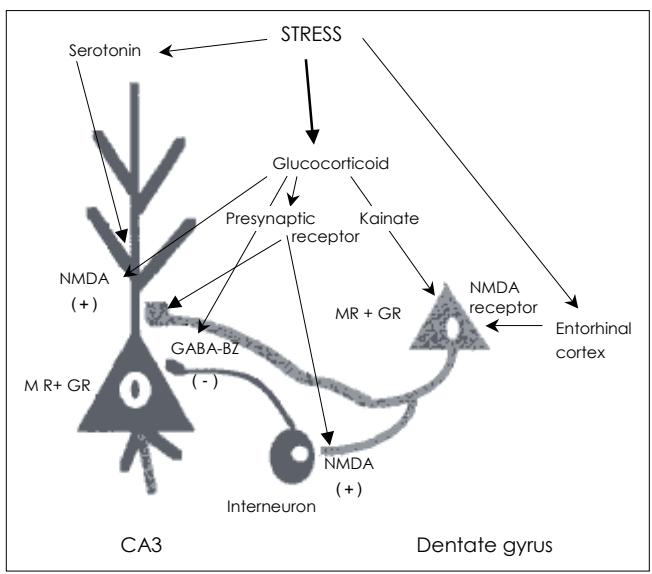


Fig. 7. Schematic diagram of the role of neurotransmitters and glucocorticoids in regulating neurogenesis and dendritic remodeling in the dentate gyrus-CA3 system of hippocampal formation.

tory input) (inhibitory tone)
 phenytoin(dilantin) GABA - benzo-diazepine
 (Watanabe 1992b).
 BDNF 가
 (Duman 2000).
 BDNF 가
 (Smith 1995 ; Nibuya 1999).
 , 가
 5 - HT_{2A} 가
 BDNF 가
 (Vaidya 1997).
 , 가
 5 - HT_{2A} , 5 - HT_{2A}
 GABA ,
 GABA ,
 가 BDNF ,
 5 - HT_{2A} 가 BDNF 가
 . BDNF ,
 , BDNF
 가 ,

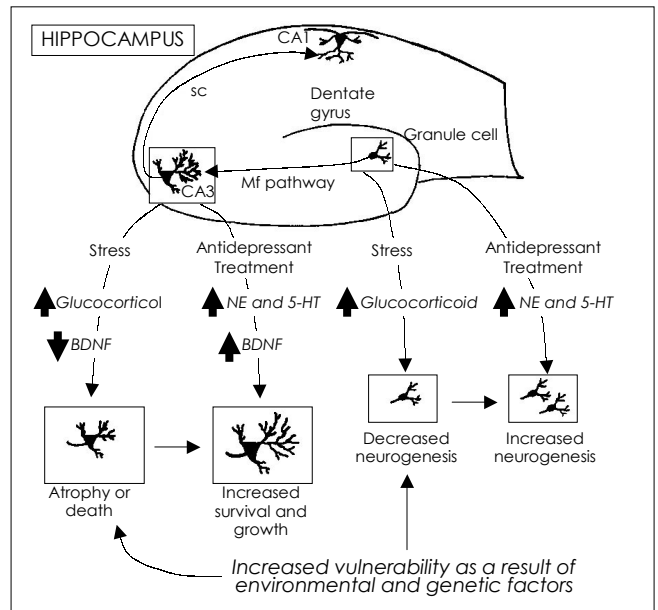


Fig. 8. A neurotrophic model for actions of antidepressant treatment and the pathophysiology of stress related disorder.

우울증과 신경가소성

1. 해마의 neurotrophic hypothesis

neurotrophic model
 (8).
 가 , BDNF ,
 CA3
 . CA3 (, , ,
 ,)
 가 . Neurotrophic hy-
 가 (Duman 가
 1997). 가 가

(volume)
 3 (MRI)
 (Sheline 1999 ; Bremner 2000 ; Mervaala 2000).
 (Sheline 1999 ; Brenmer 2000)
 가 ,
 (glucocorticoid neurotoxicity)
 가
 (glucose transporter)
 가
 (calcium excitotoxicity)
 (Sapolski 1996 ; McEwen 1999).
 HPA
 가
 (neuronal loss) (Leve-
 renz 1999), hypercortisolism
 (Cushing 's syndrome)
 가 가 (Starkman 1999)

가

가

가

가

(glial cell)

BDNF

(Sapolski 2000, Sheline 2000).

(Ongur 1998 ; Rajkowska 1999)

가

entorhinal cortex (Drevets 2000)

(White Price 1993),

가

(Carmichael Price 1995)

가

가

, BDNF neurotrophic factor

가

(Ransom Sontheimer 1992).

가

BDNF

(Duman 1999).

3. 우울증의 신경해부학 회로

2. 전전두엽의 신경원-교세포의 변화

가

가

(prefrontal cortex ; PFC)

(Drevets 1997).

가

(hippocampus),

(amygdala),

(caudate nucleus),

(putamen),

(frontal cortex)

(limbic - cortical - striatal - pallidal - thalamo-

subgenual PFC (glial cell) (Ongur 1998),

mic tract)가

(neuroa-

PFC (orbitofrontal cortex)

natomical circuit)

(Sheline 2000).

가 (Rajkowska 1999).

가

(Mayberg 1997),

(dorsolateral prefrontal cortex)

가 (Bremner 1997).

(Gould 1999)

(consolidation)

가 (explicit memory)

가

(McEwen 2000).

(prefrontal cortex : PFC)

(amygdala)

가

PFC

(working memory),

가

Rajkowska (2000)

가

(Drevets 1992).

PFC가

(basal ganglia),

(thalamus),

(ventral teg-

mental area), (dorsal raphe nucleus), (locus coeruleus)

(Nishijo 1988).

line 1998)

(Drevet 2000)

(She-

(anhedonia)

(anergy)

sweetened water consumption model

sweetened water consumption

(Muscat 1990).

(mesolimbic dopamine system)

(ventral tegmental area)

(nucleus accumbens)

(reward)

(motivation)

(re-

가

가

가

가

가

가

(substrate)

4. 아동기의 부정적 경험과 corticotropin releasing factor (CRF) 가설

(early adverse experience)

가

가 Corticotropin releasing factor(CRF)

(hyperactivity)

(reactivity) 가

(Nemeroff 1996). CRF

, CRF

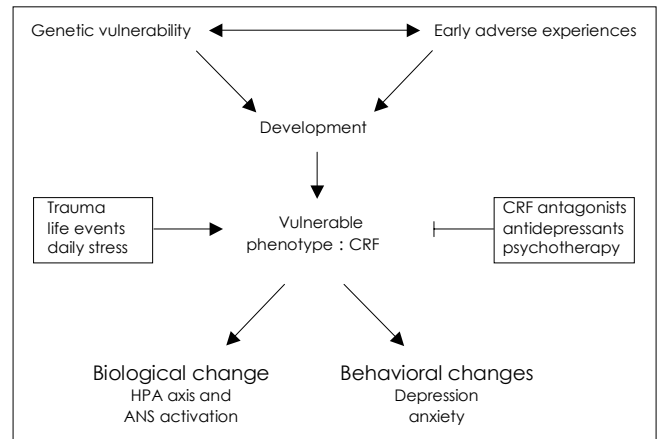


Fig. 9. The relationship between early life stress, sensitization of corticotrophin-releasing factor(CRF) neuronal systems, and the development of depression and anxiety.

. CRF 가
CRF

(phenotype)

(Heim Nemeroff 1999)(9).

(early maternal separation)

(maternal deprivation)

CRF 가, NE

5 - HT 가

, GABA/benzodiazepine

(Kaufman

2000).

CRF

(hyperactivity)

1) CRF

가, 2)

3)

CRF

, 4)

(hypothalamus)

(paraventricular nucleus ; PVN) CRF

CRF mRNA 가, 5)

가

(Arbolelius 1999).

Corticotropin releasing factor (CRF) PVN

(anterior pituitary gland)

adrenocorticotropin hormone (ACTH)

가 hypothalamo - pituitary - adrenal

(HPA) axis

CRF

(amygdala)

CRF

가 (Nibuya 1996). ,
(morphin, cocaine, haloperidol) CREB
, CREB
cAMP - CREB
, 가 (striatum) (locus
coeruleus) CREB 가 가
(Konradi 1994 ; Widnell 1994). CREB가
(region - specific
manner)
CREB CRE
transgenic model (Thome
2000) CREB (promoter) tandem
CRE reporter gene
CRE - LacZ transgenic mice
(, , ,)
CREB CRE 가
, (ECS)
buya 1995 ; 1996). , BDNF mRNA CREB가
가 .
cAMP - CREB BDNF
, . BDNF
(learned
helplessness) 가 (Siuciak 1997). BDNF
5 - HT NE
, (Kang
Schuman 1995 ; Levine 1995 ; Mamounas 1995).
가
, CREB
, 가
, 가
, PKA
(tyrosine hydroxylase)
(Melia 1992) 가
CREB
, CREB
, 가
(Dowlatshahi 1998).
CREB
, CREB
가 , CREB

가 . ,
가 cAMP
. 가
2. Rsk-CREB와 Bcl-2 유전자 발현
MAP kinase Rsk
(3). - AR
MAP kinase
(Luttrell 1999 ;
CREB
HT_{1A} G
Mendez 1999). NE HT
CREB
가
CREB BDNF
Bcl - 2 가 Rsk 가
Bcl - 2 가
(Chen 1999). ,
가 Bcl - 2 Rsk
가
(programmed cell death)
(BAD 가 Bcl - 2
))
(Rsk CREB)
EB 가 (Dowlatshahi 1998)
가
(target gene)
, 가
, cAMP
5 - HT NE BDNF 가
cAMP Ca²⁺ - activated
AR 5 - HT_{4,6,7}
, 가
가
(desensitization)
가 . , cAMP

. 가 , cAMP Ca²⁺ - activated kinase 1999). BDNF knockout mice가 wild -
 CREB . cAMP type mice sprouting
 cAMP phosphodiesterase(PDE4) BDNF가 ECS sprouting
 rolipram 가, , BDNF sprouting
 BDNF
 rolipram sprouting ,
 PDE4 isoenzyme 가 sprouting sp-
 가 PDE 4A 4B isoform 가 routing ECS
 (Takahashi 1999)
 가 .

결론

, ,
 phosphatidyl inositol 가
 lithium 가
 ,
 가 , MAP kinase Rsk
 가 . MAP kinase 가
 . 가 , BDNF

3. 수상돌기개조의 억제 및 신경조직발생의 증가

CA3 . 가 ,
 가 tia-
 neptine CA3 . cAMP
 (Watanabe 1992a).
 (neurogenesis) 가 TrkB - MAP kinase
 (Malberg 2000) 가
 (dentate gyrus) (granule neuron) 가
 가 , 가
 , cAMP - CREB
 BDNF (Palmer 1997)
 CREB BDNF
 가

중심 단어 : 가 . . .

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