

주요우울증에서 사이토카인-세로토닌 상호작용에 의한 신경변성 가설

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김 용 구

A Neurodegenerative Hypothesis of Cytokine-Serotonin Interaction in Major Depression

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A growing body of evidence suggests that major depression is associated with increased productions of pro-inflammatory cytokines such as IL-1, IL-6, IL-12 or TNF-alpha and increased concentrations of prostaglandin E2 and negative-regulatory cytokines such as IL-4 or IL-10. In major depression, interactions among brain 5-HT levels, the activity of its autoreceptors, and that of postsynaptic receptors play a critical role in mood changes and depression. Recently, the link between cytokines and serotonergic turnover has been explored. Cytokines such as IL-1, IL-2 and IFN-gamma reduce the production of 5-HT by stimulating the activity of indoleamine-2,3 dioxxygenase (IDO), an enzyme which convert tryptophan, the precursor of 5-HT to kynurenine. The kynurenine is metabolized into quinolinic acid (quinolinate) and kynurenic acid (kynurenate), an excitotoxic NMDA receptor agonist and the antagonist of three ionotropic excitatory aminoacid receptors, respectively. The cytokine-serotonin interaction through IDO that leads to the challenge between quinolinate and kynurenate in the brain may finally induce the neurodegeneration in depression. The neurodegeneration hypothesis of depression can explain how people cope with psychological or physical stress at different stages according to severity and duration of stress and why major depression develops. (J Korean Neuropsychiatr Assoc 2004;43 (4) :386-392)

KEY WORDS : Serotonin · Cytokine · Neurogenesis · Neurodegeneration · IDO · Depression.

서 론

가

가

가

¹⁾

가

³⁾

가

²⁾ 가 ,

reserpine

1950

15%

가

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reserpine

가

가

가 가 (monoamine depletion hypothesis)⁴⁾

가

가

(serotonin ; 5-HT) (norepinephrine ; NE) 가

가 (structural plasticity) (neuronal adaptation) 가

가

가

가

가

가

가 (neurodegenerative hypothesis)

세로토닌과 우울증

가 (monoamine hypothesis) 가

(turnover) 가 5-HT2 가 (up-regulation) 가

가 (autoreceptor) (presynaptic) (somatodendritic) 가

(firing) (turnover) 5-HT1B 5-HT1D 가 5-HT1A 가 pindolol 가

5-HT1D 가 5-HT1B (dorsal raphe nucleus) 가

5-HT2A, 5-HT2A (receptor binding), 5-HT2C (desensitization) 가 HT2C postsynaptic 5-HT1A (median raphe nucleus) 5-HT1A (dorsal hippocampus) (binding potential) 5-HT1A 사이토카인과 우울증

IL-2, IFN- (apathy), (mental slowing), (anhedonia), (helplessness), (dy-sphoria) 가 IL-1, IL-6, IFN- 가 IL-1, IL-6, IL-12, TNF-alpha pro-inflammatory cytokines, prostaglandin E2, negative immuno-regulatory cytokines 가 hypothalamic-pituitary adrenal (HPA) / hypothalamic corticotropin-releasing hormone(CRH), pituitary adreno-corticotropic hormone(ACTH), adrenal steroidogenesis HPA axis tryptophan kynurenine indoleamine-2,3-dioxygenase(IDO) (monocyte) (macrophage) pro-inflammatory cytokines (chemotaxis) anti-inflammatory cytokines In vitro clomipramine, sertraline, trazodone 가 IFN- IL-10 가 clomipramine, imipramine, citalopram lipopolysaccharide IL-1, IL-6, TNF- IL-2 IFN- IL-1 mRNA IL-1 receptor antagonist mRNA 가 6~112 가 HPA pro-inflammatory

cytokines (52)
 IL - 1 IL - 6 pro-inflammatory cy-
 tokines가 (paraventricular nucleus)
 CRH , HPA
 ACTH ,
 IL - 1 가
 , (10,52)
 (glucocorticoid resis-
 tance)

가 IDO L - tryptophan
 L - hydroxytryptophan, 5 - HT, melatonin
 (55) , , ,
 IL - 1, IL - 2, IFN - , TNF - , IL - 12 IDO
 가 가 (63 - 65)
 IDO kynurenine ,
 kynurenine - 3 - monooxygenase, kynureninase, kynu-
 renine aminotransferase 3 - hydroxy-
 kenurenine, anthranillic acid, kynurenate
 (Fig. 1). kynurenine - 3 - monooxygenase kynureni-
 nase IFN - TNF - . anth-
 ranillic acid quinolinic acid , qui-
 nolinic acid(quinolinate) excitotoxic NMDA receptor
 agonist (66) , kynurenic acid(kynu-
 renate) ionotropic excitatory aminoacid receptor
 antagonist (67) NMDA

사이토카인-세로토닌 상호작용과 우울증

. 가 , IL - 1
 가,
 5 - HT 가,
 가 (53) , pro -
 inflammatory cytokines 5 - HT system
 (54,55) IL - 1 , IFN - ,
 TNF - pro-inflammatory cytokines
 , , (56)
 IL - 1 5 - HT 가 ,
 IL - 1 가
 (35) , in vitro IL - 1 가 5 - HT
 5 - HT (transporter) 가 (57)
 ,
 IL - 1 가 가
 , IL - 2 TNF - , IFN -
 가 (58,59)
 TNF -
 (60) , IL - 1, IFN -
 indoleamine - 2, 3 -
 dioxygenase(IDO) 가 (61,62)

NMDA (68,69)
 , 5 - HT
 quinolinic acid
 kynurenic acid

우울증에서 신경변성 가설 (Neurodegeneration Hypothesis)

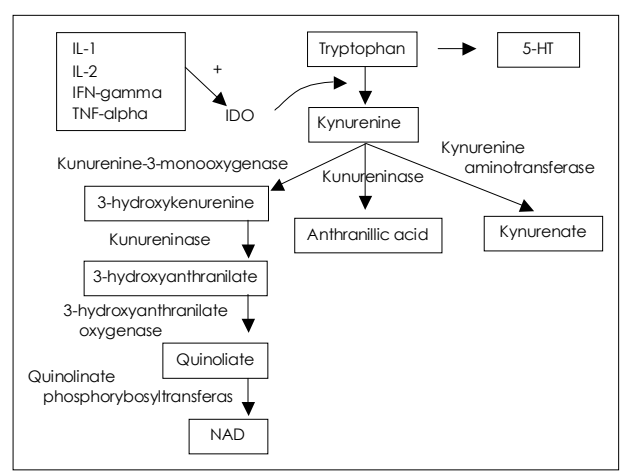


Fig. 1. Cytokine-Serotonin interaction through indoleamine-2,3 dioxygenase (IDO).

가 (70),
 가 (71-73)
 가
 가?
 가 “
 가 (74) (Fig. 2).
 (psychological stress)

가, pro-inflammatory cyto-
 kines 가 (physical stress)
 가 pro-inflammatory cyto-
 kines 가 . pro-inflammatory cyto-
 kines 가 anti-inflammatory cyto-
 kines 가
 pro-inflammatory cytokines 가
 sickness behavior가,
 pro-inflammatory
 cytokines 가 IDO 가,
 kynurenine 가

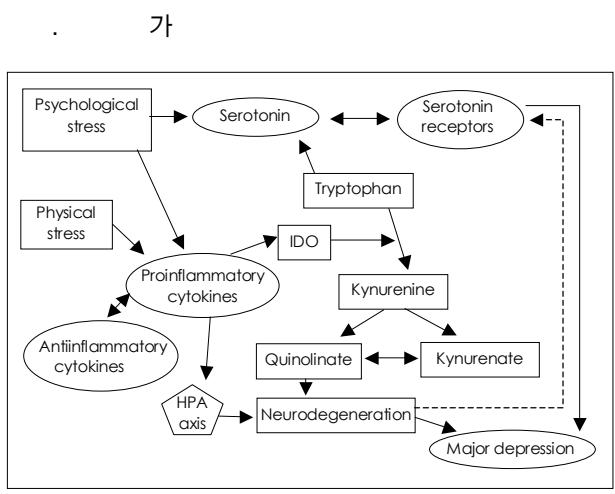


Fig. 2. Neurodegeneration hypothesis of major depression.

quinolinate
 kynurenate가
 pro-inflammatory cytokines
 anti-inflammatory cyto-
 kines
 kynurenine
 가

가
 가
 가 (75,76)
 가
 가
 가
 가
 가
 가 (77)

가 (78,79)
 가
 가
미래의 연구 방향
 가

가

중심 단어 :

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