THE TISSUE PLASMINOGEN ACTIVATOR/PLASMIN SYSTEM MAY ACT THROUGH CLEAVAGE OF PRO-BDNF TO INCREASE RISK OF SUBSTANCE ABUSE

To the Editor:

Substance abuse is a complex trait that is influenced by neurobiological, psychosocial, and environmental factors. While the ventral tegmental area/nucleus accumbens dopamine system is crucial to acute reward and the initiation of addiction, evidence suggests that permanent neuroplastic changes occur at the cellular and molecular levels that underlie the addictive process.[1] The tissue-type plasminogen activator (tPA)/plasmin proteolytic cascade is known to be important for thrombolysis. However, recent evidence has uncovered new roles for this cascade in numerous aspects of synaptic plasticity and in the pathogenesis of substance abuse. For example, a single injection of morphine induced tPA mRNA and protein expression in the nucleus accumbens of mice.[2] In the same study, morphine-induced conditioned place preference and hyperlocomotion were significantly reduced in tPA-knockout mice; the defect of morphine-induced hyperlocomotion in tPA-knockout mice was reversed by microinjections of either exogenous tPA or plasmin into the nucleus accumbens. Furthermore, other drugs of abuse such as methamphetamine,[3] nicotine,[4] and ethanol[5] increase tPA expression and activity in the nucleus accumbens, and behavioral analyses of tPA-knockout mice revealed that the tPA/plasmin system plays a crucial role in the rewarding effects of methamphetamine[3] and nicotine.[4]

The above findings suggest that the tPA/plasminogen system could be regarded as a pro-addictive factor for substance abuse. However, the mechanisms underlying this substance abuse risk induced by the tPA/plasminogen system are poorly understood. The regulation of dopamine release evoked by morphine and nicotine in the nucleus accumbens by the tPA/plasminogen has been proposed as a possible mechanism.[2–4] It has been recognized recently that drugs of abuse influence neuronal plasticity, possibly via the mechanisms of long-term potentiation, which enhances the dopamine transmission or activation in ventral tegmental area. In this report, we proposed that the role of tPA/plasmin in risk of substance abuse may arise from their action on brain-derived neurotrophic factor (BDNF) to influence the neuroplastic change in this respect.

BDNF is a member of the neurotrophic factor family and is the most abundant neurotrophin in the brain. BDNF plays a key role in the neuronal plasticity and survival of midbrain dopaminergic neurons.[6] Evidence from animal and clinical studies suggests that increased brain BDNF activity may be implicated in the pathogenesis of substance abuse. For example, BDNF infusion into the rat midbrain enhances the rewarding effects of cocaine, as measured by the condition place preference paradigm, and cocaine-conditioned place preference was reduced in heterozygous BDNF-knockout mice.[7] Using a rat model of drug craving, it was found that the responsiveness to cocaine cues progressively increased over the first 60 days of cocaine withdrawal, and that BDNF levels within the mesolimbic system progressively increased after cocaine withdrawal. This suggests that increases in BDNF levels may lead to synaptic modifications that underlie enhanced responsiveness to cocaine cues after prolonged withdrawal periods.[8] Similarly, a single intra-VTA infusion of BDNF induced a long-lasting enhancement of cocaine seeking for up to 30 days, suggesting that BDNF-mediated neuroadaptations in the midbrain are involved in cocaine-seeking behavior after withdrawal.[9] In humans, the 66Val allele of the BDNF Val66Met polymorphism is associated with higher BDNF secretion in response to neuronal stimulation compared with the 66Met allele. We found a higher BDNF 66Val homozygote frequency in people with substance abuse as compared with normal controls.[10]

In the nervous system, the proteolytic cleavage of pro-BDNF, a BDNF precursor, to (mature) BDNF occurs specifically through the tPA/plasmin pathway.[11] Given that pro-BDNF and mature BDNF have distinct and sometimes opposing functions, the processing of these molecules in the tPA/plasmin pathway is central to determining the direction of BDNF action in neuronal plasticity.[12] Thus, the increased tPA levels or activity by drugs of abuse such as morphine, methamphetamine, nicotine, and ethanol may enhance the proteolytic cleavage of pro-BDNF to mature BDNF, which then increases midbrain neuroplastic changes associated with drug addiction. This proposal represents the integration of both systems in the mechanism of substance abuse and may provide a novel strategy for the treatment of substance abuse.

Sincerely,

Cheng-Dien Hsu, MD

Shih-Jen Tsai, MD

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Dr. Hsu is chief of the Department of Psychiatry at Taiwan Adventist Hospital in Taipei. Dr. Tsai is attending psychiatrist in the Department of Psychiatry at Taipei Veterans General Hospital and associate professor at the School of Medicine at National Yang-Ming University in Taipei, Taiwan.

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Please direct all correspondence to: Shih-Jen Tsai, MD, Department of Psychiatry, Taipei Veterans General Hospital, No. 201 Shih-Pai Road, Sec. 2, 11217, Taipei, Taiwan; Tel: 886-2-28757027 ext. 276, Fax: 886-2-28725643; E-mail: sjtsai@vghtpe.gov.tw.

DIMENSIONAL PSYCHOPATHOLOGY AND VULNERABILITY TO PSYCHOSIS: *ENVISAGING THE THIRD GENERATION OF PRODROMAL/ULTRA HIGH-RISK MODELS*

To the Editor:

Early identification of psychosis is one of the fields of contemporary psychiatry where pioneering efforts to promote evidence-based practices is closely coupled with an original, translational-oriented concept development.[1-3] Gradually, in the last 15 years, the focus has moved from timely

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