Molecular Mechanisms of Psychostimulant Addiction

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Drug addiction represents a pathological form of neuroplasticity along with the emergence of aberrant behaviors involving a cascade of neurochemical changes mainly in the brain's *rewarding* circuitry. The aberrant behavioral phenotypes can be assessed by an animal model of drug-induced behavioral sensitization, which is characterized by an *initiation* stage that is formed in the ventral tegmental area and a behavioral *expression* stage determined mainly in the nucleus accumbens. Numerous studies during past decades demonstrate that the mesocorticolimbic dopamine pathway plays an essential role in the development of behavioral sensitization. Moreover, a series of cellular signaling pathways and gene expression determine the severity of addictive behaviors. In addition to the well-characterized dopamine D_1 receptor-mediated cAMP/protein kinase A up-regulation in the nucleus accumbens, recent reports indicate the cellular mediator dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) and transcription regulator ΔFosB are associated with the accumbal PKA pathway to modulate the development of behavioral sensitization. The finding of cAMP-independent and dopamine D_2 receptor-mediated Akt/GSK3 in activation in the nucleus accumbens of behaviorally sensitized animals implies that a signal cascade down-stream of both dopamine D_1 and D_2 receptors comprises the mainstay of the addiction network. This review outlines the cellular pathways that have been demonstrated to participate in psychostimulant addiction, focused particularly in the nucleus accumbens. *(Chang Gung Med J 2009;32:148-54)*

Key words: drug addiction, (meth) amphetamine, dopamine, glutamate, nucleus accumbens

Drug addiction could be simply defined as an abnormal behavioral outcome, i.e. after repetitive drug intake, the addict experiences compulsive drug intake, despite profound adverse effects.[1,2] Prolonged use of abused drugs, such as morphine, cocaine, (meth) amphetamine, cannabinoids or alcohol may contribute to behavioral abnormalities that can last for months or even years after discontinuation of drug consumption.[3] Animal models that simulate this behavioral phenotype by repeated administration of the drug, usually result in an enhanced behavioral response during subsequent drug exposure.[4] This phenomenon is called behavioral sensitization, which is recognized as an enduring structural change and also a form of drug-induced neural plasticity.[5] Over the past decade, numerous studies have provided fruitful information regarding the potential substrates underlying the development of drug-triggered behavioral sensitization. These include various membrane receptors, cellular signaling pathways and nuclear gene expression.[1,6] Understanding the molecular mechanism of behavioral sensitization would help us to develop therapeutic programs against drug addiction and/or relapse. This review briefly outlines the essential neural circuitry and cellular mechanisms that are currently known to play a central role

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in psychostimulant-induced behavioral sensitization, especially with cocaine and (meth) amphetamine.

Role of mesocorticolimbic dopamine and glutamate in behavioral sensitization

The mesocorticolimbic dopaminergic pathway, which originates from the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc), amygdala, prefrontal cortex (PFC) and other forebrain regions, plays an essential role during the development of behavioral sensitization.[4,7] The early action of psychostimulants in the VTA is considered to be a critical cellular event for initiation of behavioral sensitization.[7] After repetitive drug exposure, the neural circuitry in the ventral striatum (mainly the NAc) is recruited for behavioral expression.[8] According a previous report, rats receiving repeated doses of amphetamine in the VTA exhibited potentiated locomotor responses to peripheral or intra-accumbens administered amphetamine.[9] Conversely, repeated administration of amphetamine into the NAc increased locomotor activity, but could not sensitize the locomotor effect to systemic amphetamine injections.[10] It is thus concluded that neurons in the VTA are crucial for the induction (or initiation) phase of amphetamine sensitization, while the NAc (shell and core) is essential for its behavioral expression.[11] In the VTA, enhanced dopamine neuronal activity is an essential step for consequent behavioral changes. Furthermore, a list of receptors that are known to modulate VTA dopamine activity may affect the severity of behavioral sensitization. For instance, antagonists of dopamine D_1 and glutamate N-methyl-D-aspartate (NMDA) receptors or agonists of $GABA_B$ receptors administered locally in the VTA could arrest the induction of amphetamine sensitization.[12,13] During behavioral expression, the VTA dopamine activity returned to the basal level, however enhanced dopamine release in the NAc, particularly at late withdrawal time, contributed to behavioral augmentation.[14] The persistent dopamine release in the NAc along with induction of preproenkephalin and preprodynorphin expression suggests that enduring postsynaptic neuronal events occurr during amphetamine sensitization.[15]

In addition to dopamine,[16] a glutamate-dependent cellular mechanism is also involved in the neuroadaptative processes of drug addiction. In particular this is true in regard to drug-associated learning and memory.[17] Glutamatergic neurons, mainly from the PFC and other limbic regions innervate both the VTA and NAc, where glutamate either drives dopamine activity or modulates the neuronal activity of dopamineceptive neurons (median spiny neuron; MSN), respectively.[18] The requirement of glutamate to activate midbrain dopamine transmission led to the findings that long-term potentiation (LTP) could be formed in both VTA dopamine neurons and MSN of the NAc.[16,19] This sensitized neuronal event is postulated to be mediated through enhanced AMPA glutamate receptor responsiveness, which requires the induction of GluR1 and/or GluR2 receptor subunits and altered AMPA receptor trafficking.[20] The facts that NMDA antagonist prevented both LTP and behavioral sensitization, and that drug-induced LTP in behaviorally sensitized animals simulates LTP formation in the hippocampus during learning/memory or epilepsy, suggest that drug addiction can be viewed as a form of neuronal plasticity.

The involvement of cAMP-PKA-CREB-ΔFosB signal in psychostimulant-induced behavioral sensitization

In the NAc, both dopamine D_1- and D_2-like receptors as well as glutamate NMDA and AMPA receptors located on the MSNs are primary targets for altered neurotransmission upon amphetamine or cocaine challenge.[15,21] In behavior-sensitized animals, D_1 dopamine receptor supersensitivity occurs in the NAc.[22] This cellular event could affect the down-stream Gs protein coupling and induce up-regulation of adenylyl cyclase and protein kinase A (PKA) signals. Consequently, the D_1 dopamine receptor-mediated cellular signaling cascade would enhance phosphorylation of the transcription factor cAMP response element binding protein (CREB) and the expression of immediate-early genes, such as Fos, Jun and ΔFosB.[23,24] Induction of expression of these genes is rapid and mostly transient, and forms homo- or hetero-dimmer in order to bind to the AP-1 binding site (with a consensus sequence of TGA(G/C)TCA) to evoke subsequent gene expression.[25] Activation of CREB by phosphorylation at Ser133 by PKA and other protein kinases is a common neuronal adaptation in the NAc to psychostimulants.[26] Once phosphorylated, CREB forms a dimer and binds to specific CRE sites of target genes, such as dynorphin.[27] Previous studies suggest that drug-

induced CREB activation/phosphorylation in the NAc comprises a negative feedback mechanism which dampens behavioral sensitivity to subsequent drug exposure.[28] In support of this notion, phospho-CREB-induced dynorphin in the NAc was found to bind to κ opioid receptor through a receptor-mediated aversive reaction to produce an antagonistic effect on measures of drug reward.[29] On the other hand, ΔFosB (a Fos family protein) accumulation in the NAc represents a universal phenomenon after chronic exposure to various abused drugs. It is known that over-expression of ΔFosB in the NAc increases the behavioral response to cocaine and amphetamine. Additionally the amount of ΔFosB accumulation in the nucleus determines the duration and intensity of drug-induced behavioral sensitization.[30] Similar to the effects of CREB transcription factor, over-expression of ΔFosB induces the AMPA GluR2 subunit in the NAc, which accounts for the reduced sensitivity of NAc neurons to glutamate.[31] Hence, similar to CREB-regulated dynorphin, ΔFosB – regulated GluR2 expression represents an alternative negative feedback pathway to compensate for the heightened behavioral sensitization. Since the ultimate changes occur at the transcriptional level, dopamine D_1 receptor-mediated nuclear signaling is viewed as a predominant factor for long-lasting behavioral sensitization.

Significance of DARPP-32 and Cdk5 in drug addiction

As addressed above, it is well known that a significant portion of behavioral changes after chronic psychostimulant treatment is mediated through striatal dopamine D_1 receptors.[32,33] Down-stream of D_1 receptor-mediated cAMP accumulation and PKA activation, a cellular substrate named DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of 32 kDa) plays an important role in D_1 receptor-dependent neuronal function.[6] DARPP-32, which is enriched in both the dorsal (nucleus caudate/putamen) and ventral striatum, can be phosphorylated by PKA at Thr34 thus converting this molecule into a potent inhibitor of protein phosphatase-1 (PP-1).[34] Acute stimulation with cocaine or methamphetamine activates the dopamine D_1 receptors, consequently leading to DARPP-32/Thr34 phosphorylation in the striatum.[35,36] Several studies have shown that DARPP-32 participates in the progressive development of behavioral sensitization to cocaine and amphetamine.[6] Knock-out of DARPP-32 or DARPP-32 mutation (threonine 34 was replaced by alanine) in mice attenuated the hyperlocomotor activity induced by acute cocaine treatment.[37,38] Moreover, chronic treatment with cocaine or methamphetamine decreased Thr34, but increased Thr75 phosphorylation.[35,39] This latter effect was due to enhanced Cdk5 (a cellular kinase that phosphorylates DARPP-32 at Thr75 residue) activity driven by trafficking of the Cdk5 activator, p35, from the cytoplasm to the cell membrane.[39] Keeping in mind that DARPP-32/Thr75 phosphorylation would inhibit the PKA activity,[40] it was postulated that chronic treatment of psychostimulants via Cdk5 activation and DARPP-32/Thr75 phosphorylation would inhibit PKA-dependent signaling. This represents a homeostatic feedback mechanism to counterbalance the over-reactive cAMP/PKA/DARPP-32/Thr34 signaling and behavioral sensitization. In agreement with this hypothesis,[41] inhibition of Cdk5 has been found to enhance cocaine-induced behavioral sensitization.[35]

Significance of Akt/GSK-3 signaling in behavioral sensitization

Other than classical dopamine D_1 receptor-mediated cAMP-PKA-DARPP-32 and nuclear CREB-ΔFosB signaling, recent investigations have shown that dopamine D_2-like receptors initiate a cAMP-independent pathway that affects the development of behavioral sensitization.[42] Initial studies of dopamine transporter (DAT)-knockout mice revealed that persistent elevation of extracellular dopamine levels led to a reduction of Akt phosphorylation as well as activity in these spontaneously hyperactive mice.[43] The inactivation of Akt in these mice reduced the phosphorylation levels of its down-stream substrates, GSK-3α and GSK-3β, thus activating GSK-3 activity in the striatum.[43] The evidence that the antipsychotic haloperidol caused enhanced Akt phosphorylation and reduced GSK-3 activity in wild-type mice indicates that striatal Akt-GSK3 signaling is regulated through dopamine D_2 receptors under physiological conditions.[44] Interestingly, administration of amphetamine also results in an inhibition of Akt phosphorylation/activation.[45] This not only confirms the regulation of Akt-GSK3 by dopamine input but also suggests that

this signaling pathway participates in psychostimulant-induced behavioral activation. In concert with this notion, a GSK-3 inhibitor was demonstrated to reduce hyperactivity in both DAT-knockout mice and amphetamine-treated wild-type mice.[43,46] Genetically engineered GSK-3β heterozygote mice exhibited a diminished behavioral response to amphetamine compared to wild-type mice, while constitutively active GSK-3β mutants exhibited locomotor hyperactivity. Both lines of evidence support the idea that the Akt-GSK3 pathway is involved in dopamine-dependent behavior. Recently, a human genetic study that associated Akt1 haplotypes with schizophrenia suggested that loss of Akt1 function in schizophrenia may be a cause of aberrant behaviors.[44] Finally, Akt and GSK-3 have been associated with the action of the anti-mania drug lithium, which is an inhibitor of GSK-3 but also an Akt activator.[47,48] Administration of lithium inhibits brain GSK-3 activity in mice, and in turn suppresses dopamine-dependent locomotor hyperactivity.[43] Whether the dopamine D_2 receptor-dependent Akt-GSK-3 pathway is involved in the development of psychostimulant-induced behavioral sensitization remains unclear and requires further investigation.

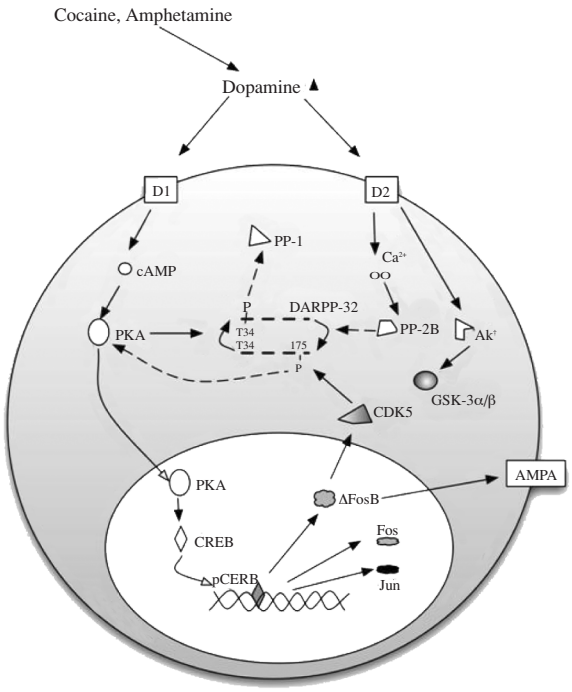

Fig. 1 Schematic diagram illustrates the essential signal transduction pathways which underlie dopamine D_1 or D_2 receptor-mediated cellular events. Amphetamine or cocaine blocks the dopamine transporter, and in turn enhances the synaptic dopamine concentration. Activated D_1 receptor mediates through a cAMP-dependent signaling, includes DARPP-32/Thr34 phosphorylation and PKA translocation to evoke a nuclear signal cascade, and eventually increases the expression of glutamate AMPA receptor and cellular Cdk5 activity. Cdk5 then phosphorylates DARPP-32/Thr75 to dampen the PKA signaling. On the other hand, dopamine D_2 receptor mediates through a cAMP-independent pathway of Akt-GSK3 activation, synergistically strengthening behavioral sensitization. (*see text for details and abbreviations*) Solid lines indicate stimulating effects; dashed lines represent inhibitory effects.

Prospective treatment against drug relapse

In conclusion, understanding the molecular mechanisms of behavioral sensitization as indicated in the Fig. 1 would facilitate the discovery of drug therapy programs against addiction. However, most of the clinical progress in addiction treatment is focused on the elimination of physical dependence and withdrawal syndromes, and does not target the core symptoms of addiction, i.e. drug craving and relapse (manifested by either drug cues or stress)[49] during abstinence.[23] Treatments have attempted to block the drug targets, such as the use of naltrexone for opioid addicts/alcoholics or the development of cocaine or nicotine vaccines, or to modulate receptor activity (receptor agonist or partial agonist).[23,50] The latter is the opposite of the target blockade concept, however its efficacy has been demonstrated against opioid (methadone) and nicotine (nicotine patch or chewing gum) addiction. Unfortunately, at present there is no available method to treat psychostimulant craving and relapse through the known molecular mechanism. Considering the general concept that midbrain DA is essential for the development of drug addiction, several DA agonists and antagonists have been tested. The results demonstrate that although DA antagonists can block acute drug-induced behavioral activation, they cannot limit drug craving.[51] On the other hand, D_1 agonists or D_2 partial agonists were able to reduce cocaine craving and relapse in animal studies.[52] These facts reflect that a thorough understanding of the molecular mechanism in behavioral sensitization to psychostimulants could effectively translate into a therapeutic drug program against drug addiction.

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成癮性興奮藥物的分子作用機制

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藥物成癮是一種神經可塑性的改變，涉及大腦內部成癮迴路中物性與化性的變異，因而影響到個體外觀的行爲表徵。過去在動物實驗上的諸多研究，讓我們有機會得以窺視建構「藥物成癮」的分子作用基礎。本篇文章利用興奮性藥物當作例子，說明安非他命類物質成癮所涉及的神經傳導物質以及訊號傳遞；首先以成癮迴路中多巴胺－麩胺酸－GABA 神經間的互動做基礎，再探討由多巴胺第一亞型 (D_1) 受體所啓動的 cAMP-PKA-CREB-ΔFosB 訊息以及由多巴胺第二亞型受體策動的 Akt/GSK3 訊號在成癮的動物模式－行爲致敏化形成時所扮演的角色。最後，介紹個體對藥物成癮所誘發的負迴饋訊號 Cdk5-DARPP32 的作用機制，並藉由目前對這些作用機轉的瞭解探討可能研發的藥癮治療方式。(長庚醫誌 2009;32:148-54)

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