Sim *et al.*
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REVIEW

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Cellular messenger molecules mediating addictive drug-induced cognitive impairment: cannabinoids, ketamine, methamphetamine, and cocaine

Hye In Sim[1†], Dae Hyun Kim[1†] and Mikyung Kim[1,2*]

Abstract

Background: Cognitive impairment is a commonly reported symptom with increasing life spans. Numerous studies have focused on identifying precise targets to relieve or reduce cognitive impairment; however, its underlying mechanism remains elusive. Most patients or animals exposed to addictive drugs exhibit cognitive impairment. Accordingly, the present review discusses the molecular changes induced by addictive drugs to clarify potential mechanisms that mediate cognitive impairments.

Main body: We investigated changes in cognitive function using four drugs: cannabinoids, ketamine, methamphetamine, and cocaine. Chronic administration of most addictive drugs reduces overall cognitive functions, such as working, spatial, and long-term recognition memories. Levels of several transcription factors involved in neuronal differentiation, as well as functional components of neurotransmitter receptors in neuronal cells, are reportedly altered. In addition, inflammatory factors showed a generally increasing trend. These impairments could be mediated by neuroinflammation, synaptic activity, and neuronal plasticity.

Conclusion: This review outlines the effects of acute or chronic drug use and potential molecular alterations in the central nervous system. In the central nervous system, addictive drug-induced changes in molecular pathways associated with cognitive function might play a pivotal role in elucidating the pathogenesis of cognitive impairment.

Keywords: Cognitive impairment, Addictive drug, Neuroinflammation, Neurodevelopment, Oxidative stress

Background

With increasing average life expectancy, the number of individuals living with cognitive impairment is growing, due to various conditions such as degenerative disorders [1]. Moreover, as lifespan increases, cognitive functions greatly affect the quality of life. Unfortunately, the underlying cause of most cognitive impairment-related disorders remains unclear [2, 3]. Drugs such as rivastigmine, donepezil, and memantine have been developed and are indicated to treat cognitive impairment. However, currently available therapeutic agents only afford minimal symptomatic relief and fail to address the underlying disease. In addition, these agents can induce various side effects [4]. Therefore, there is an urgent need to develop more effective and accessible therapeutics to combat cognitive impairment.

In recent years, the population of drug abusers has been steadily growing. According to the United Nations Office for Drug Crime 2018, 265 million people worldwide use drugs, and 35 million suffer from drug use disorders [5]. Furthermore, drug users often experience side effects

*Correspondence: mkkim@syu.ac.kr
†Hye In Sim and Dae Hyun Kim have contributed equally to this work
[1] Department of Chemistry Life Science, Sahmyook University, Hwarangro 815, Nowongu, Seoul 01795, Republic of Korea
Full list of author information is available at the end of the article

such as headaches, hallucinations, and cognitive impairment. For example, amphetamine or heroin abusers can exhibit damaged spatial working memory, and methamphetamine abusers show impairments in most cognitive domains, including working memory, attention, and learning [6, 7]. These findings indicate that drug abuse may influence pathways associated with cognitive function. Thus, the purpose of this study is to find novel candidate targets that can be therapeutic agents for cognitive impairments through understanding the mechanisms of cognitive impairments by addictive drugs. To do this, the present review discussed the relationship between drug abuse and cognitive function, clarified the mechanisms of drug-induced cognitive impairment, and tried to identify new targets for effective treatment. Herein, we reviewed changes in cellular effects and cognitive functions following the administration of several addictive drugs, focusing on four select drugs based on the mechanistic classification of drugs of abuse: cannabinoids in class I (drugs that activate G-protein-coupled receptors), ketamine in class II (drugs that bind to ionotropic receptors and ion channels), and cocaine and methamphetamine in class III (drugs that bind to transporters of biogenic amines) [8].

Main text

Cannabinoids

Cannabinoids are psychoactive drugs found in cannabis and mediate their actions via a G-protein coupled cannabinoid receptor (CB_1 and CB_2) to activate cell signaling pathways [9]. Cannabinoids have been prescribed to patients with neurological disorders [10]. Moreover, cannabinoid administration in animals with cognitive impairment improved working memory and cognition [11]. However, psychotic symptoms and impaired cognition were observed in the healthy control group [12].

In the healthy control group, cannabinoid-induced cognitive defects appeared to be related to synaptic plasticity. Administration of Δ9-tetrahydrocannabinol (Δ9-THC) increased levels of serum brain-derived neurotrophic factor (BDNF) and impaired spatial working memory [13]. Additionally, cannabinoids can decrease recognition memory by increasing the mechanistic target of rapamycin (mTOR) signaling [14]. Δ9-THC-treated adolescent rats exhibited impaired social interaction and object recognition memory, mediated via upregulation of hippocampal Ras-related protein (Rab-1A) and downregulation of phosphoglycerate mutase 1 (PGAM1) [15]. Altered Rab-1A levels have been associated with synaptic dysfunction, and alterations in Ras proteins reportedly influence long-term memory [16]. PGAM1 was shown to play a role in neuronal proliferation and differentiation, and its reduced levels were detected in neurological disorders [17, 18]. Rats exhibiting cognitive impairment after THC administration also presented increased levels of inflammatory factors such as ionized calcium-binding adapter molecule 1 (Iba1), tumor necrosis factor (TNF)-α, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) [19], thereby indicating that cannabinoid-induced cognitive impairment might be influenced by neuroinflammation and oxidative stress.

It has been reported that cannabinoid administration can improve symptoms in animal models of cognitive disorders. Transgenic amyloid precursor protein mice, a representative animal model of Alzheimer's disease (AD), demonstrated improved cognitive functions after chronic cannabinoid administration by increasing brain glucose uptake, decreasing Aβ levels, and reducing protein expression of COX-2, known to induce inflammation [20, 21]. In aged male mice, impaired working memory was ameliorated following treatment with a CB_2 agonist via downregulation of specific proinflammatory cytokines, including interleukin (IL)-23, IL-27, and interferon (IFN)-β [22]. These results indicate that CB_2 agonists may afford anti-inflammatory effects and improve memory in animals with cognitive deficits. Aso and Ferrer (2016) reviewed the roles of CB_2 as a potential target in patients with AD and an animal model of AD, identifying a correlation between CB_2 and Aβ levels. CB_2 agonists improved cognitive functions in AD models via Aβ clearance, thus attenuating Aβ peptide-induced inflammation, tau protein hyperphosphorylation, and oxidative stress-induced damage [23]. In a Parkinson's disease animal model, CB_2 activation afforded neuroprotection by eliciting anti-inflammatory and antioxidant activities [24].

Ketamine

Ketamine is a hallucinogenic drug that mainly targets N-methyl-D-aspartate (NMDA) receptors [8]. Ketamine is a general anesthetic that was originally synthesized for medical use. However, ketamine has gained notoriety for non-medical purposes. In the early 2000s, repeated ketamine administration was found to be neurotoxic and cause short-term memory loss. In most cognitive tests, patients with ketamine-dependency showed significantly poorer performance in terms of verbal memory, motor speed, verbal fluency, and attention than normal controls [25].

It is well-established that ketamine is a non-competitive NMDA receptor antagonist. Administration of high-dose ketamine was found to impair learning and memory performance and increase NMDA receptor hypofunction [26]. In a study using NMDA receptor subunit (GluN2D) knockout mice, (S)-ketamine, but not (R)-ketamine, induced cognitive impairment in the novel object recognition test (NORT), whereas both (R)- and

(S)-ketamine impaired cognitive ability in wild-type mice [27]. These findings implied that NMDA receptors, especially GluN2D, could mediate (R)-ketamine-induced cognitive deficits. Furthermore, chronic ketamine exposure significantly downregulated hippocampal expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits (GluA1 and GluA2) and NMDA receptor subunits (GluN2A and GluN2B), as well as reduced the phosphorylation and mRNA expression levels of GluA1, GluA2, GluN2A, and GluN2B. Additionally, chronic ketamine administration impaired spatial learning and memory in the Morris water maze [28]. Reportedly, although protein expression and phosphorylation levels of GluA1 were elevated immediately after ketamine exposure, these were reduced approximately six months after ketamine administration. The decline in GluA1 protein expression and phosphorylation overlapped with decreased spatial working memory [29].

In addition, ketamine can affect neurodevelopment. The serum BDNF concentration was significantly lower in ketamine-treated rats than in the normal group, with the former group animals exhibiting memory deficits in the Morris water maze [30]. In human research, long-term ketamine users showed poor activation in the hippocampal complex, as well as impaired spatial memory [31]. Rats treated with high doses of ketamine showed an increased number of apoptotic cells in the hippocampal CA1 region and dentate gyrus; this group also exhibited impaired spatial learning and memory in the Morris water maze [32]. In mice treated with high doses of ketamine, neuronal cells were reduced in the hippocampal CA1 and CA3 regions, accompanied by a decrease in hippocampal dendritic spine density [33].

In contrast, ketamine impaired cognitive function by activating the cAMP response element-binding protein (CREB) signaling pathway. Ketamine-treated pregnant rats presented significantly decreased protein levels of ERK, p-ERK, protein kinase A (PKA), p-PKA, and p-CREB in the hippocampi, accompanied by impaired spatial learning and memory [33]. Chronic ketamine-exposed mice showed decreased expression and phosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKIIβ), ERK 1/2, CREB, and nuclear factor kappa-B (NF-κB) and exhibited impaired spatial learning and memory. In addition, the observed cognitive impairment was alleviated by CaMKIIβ overexpression, indicating that CaMKIIβ signaling is possibly associated with ketamine-induced cognitive impairment [28]. Ketamine-treated postnatal day 7 rats showed significantly decreased hippocampal expression of p-protein kinase C-gamma (PKCγ) and p-ERK 1/2, which impaired spatial learning and memory [32]. Activated NMDA receptors can activate CaMKIIβ and ERK 1/2, and PKA is phosphorylated via this signaling pathway. In addition, activated ERK and PKA activate CREB, transcribing various neuronal genes associated with neurogenesis and cognitive function [28, 33]. Ketamine reportedly interferes with this series of downstream processes, resulting in cognitive impairment, particularly spatial impairments, through the CREB signaling pathway.

Methamphetamine

Methamphetamine (METH) is a highly addictive central nervous system stimulant, initially synthesized from amphetamine, a widely prescribed medication for various diseases [34]. Notably, METH causes neurotoxicity and cognitive impairment.

Numerous studies have suggested that long-term METH abuse can result in various cognitive impairments. For example, METH use can impair attention, executive functions, language/verbal fluency, verbal learning and memory, visual memory, and working memory; in particular, reward- or impulse-related functions and social cognition are markedly affected [7]. However, sustained abstinence could recover global neurocognitive functions [35].

Dopamine is one of the most common causes underlying cognitive impairment. METH abusers reportedly exhibit impaired motor tasks and memory task function, with significantly reduced dopamine transporter (DAT) expression even after detoxification for 11 months [36]. In addition, METH users experience deficits in short-term memory, executive function, and manual dexterity, along with a decrease in striatal DAT binding potential [37]. González et al. (2018) reported that chronic METH administration increased mRNA expression of dopamine receptor 1 (Drd1) in the medial prefrontal cortex (mPFC) of mice, induced no change in dopamine receptor 2 (Drd2) mRNA expression, and impaired object recognition memory. Accordingly, increased Drd1 mRNA expression might lead to overaction of Drd1, with detrimental effects on cognition [38]. The Drd1 antagonist SCH 23,390 successfully suppressed METH-induced cognitive impairment in the NORT; however, the Drd2 antagonist raclopride failed to demonstrate similar benefits. These findings suggest that METH-induced cognitive impairment can be attributed to Drd1 activation [39]. In contrast, hypothalamic Drd1 protein expression decreased following METH exposure, while METH impaired spatial working memory in the radial 8-arm maze task [40]. In addition, Drd1 is associated with the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway. ERK1/2, a member of the mitogen-activated protein kinase (MAPK) family, plays a crucial role in synaptic activity and neuronal plasticity [41]. Repeated METH administration induced cognitive impairment in the

NORT and suppressed ERK1/2 phosphorylation in the PFC. Moreover, the Drd1 antagonist SCH 23,390 could overcome the suppressed ERK1/2 phosphorylation and improve METH-induced cognitive impairment [39].

Notably, glutamate receptors may also influence METH-induced cognitive impairment. METH administration increased the mRNA expression of Gria1, AMPA subunit, and Grin1, NMDA receptor subunit, in the mPFC, accompanied by impaired object recognition memory [38]. Repeated METH administration significantly decreased the intensity of NMDA receptor binding in the PFC and hippocampus. Furthermore, METH administration significantly reduced working memory in the Y-maze task and diminished learning and memory abilities in the passive avoidance test [42]. METH self-administration induced deficits in short-term and long-term memory recognition. Moreover, mGluR5 and metabotropic glutamate receptor subunit expression was significantly reduced in the perirhinal cortex [43].

METH induces neuroinflammation, leading to cognitive impairment. Increased hippocampal protein levels of IL-1β were detected in METH-exposed mice, along with impaired spatial learning in the Morris water maze. Similar to METH exposure, IL-1β exposure can induce cognitive deficits and suppress the differentiation of neural progenitor cells [44]. Chronic METH significantly increased the levels of hippocampal IL-1β and IL-6, TNF-α, Toll-like receptor 4 (TLR4), MyD88, and NF-κB phosphorylation. METH impaired spatial learning, memory, and memory recognition. TLR4 expression reportedly promotes NF-κB phosphorylation via the MyD88-dependent pathway, leading to increased nuclear transcription of inflammatory cytokines such as IL-1β, IL-6, and TNF-α [45]. Chronic METH administration increased inflammatory biomarkers, such as IL-1β and TNF-α, and induced learning and spatial memory impairments [46].

Cocaine

Cocaine is a psychoactive drug that reportedly inhibits the solute carrier family (SLC) 6A3, a known dopamine transporter, and suppresses dopamine reuptake in the synaptic cleft. Cocaine administration influences neurodevelopment, including cognitive functions. Cocaine addiction can impair most cognition-related brain areas, especially those associated with reaction inhibition, memory, reward decisions, and psychomotor performance [47].

The dopamine pathway is a representative molecular pathway altered by cocaine. Individuals with cocaine use disorder showed poor performance in the Stroop test, enhanced availability of Drd3-rich substantia nigra, and reduced Drd2-rich dorsal putamen [48]. In rats, prolonged cocaine exposure impaired sustained attention tasks and decreased mRNA expression of Drd2 in the mPFC and orbitofrontal cortex [49]. In contrast, chronic cocaine administration induced hyperactivity and increased Drd2 mRNA levels in the nucleus accumbens of rats [50].

Cocaine administration affects neurodevelopment and causes cognitive impairment. In cocaine-treated rats, the expression levels of BDNF and the high-affinity BDNF receptor decreased in the PFC or salivary glands, thus impairing cognitive functions such as working memory and fear acquisition [51, 52]. Insulin-like growth factor II (IGF-II) plays a pivotal role in cell growth, development, and regeneration and exhibits high hippocampal concentrations. IGF-II reportedly promotes long-term strengthening of hippocampal-related memories [53]. In prenatal cocaine-exposed animals, hippocampal expression of IGF-II mRNA and protein decreased, whereas methylation of cytosine-phospho-guanine dinucleotides in the differentially methylated region 2 of IGF-II increased, thus eliciting impaired spatial learning and memory [54]. Furthermore, self-administered cocaine in rats exhibited reduced hippocampal neurogenesis and lower performance in learning and memory tests [55]. Thus, reduced BDNF levels and neuronal development may play a role in cognitive impairment.

Cocaine-induced cognitive impairment is also associated with neuroinflammation and oxidative stress. Neuroinflammation causes cognitive aging and increases the generation of reactive oxygen species (ROS), thus inducing oxidative stress [56, 57]. Notably, oxidative stress is considered an underlying causative factor of neurodegenerative diseases [58]. NF-κB, c-Fos, and FosB are required for the transcription of inflammatory cytokines, such as ILs, and induce an inflammatory response [59, 60]. During inflammatory reactions, NF-κB and FosB are positively correlated, whereas superoxide dismutase (SOD) and glutathione peroxidase (GPx) elicit opposite outcomes [57]. Cocaine-dependent female subjects showed reduced executive functions and elevated plasma IL-6 levels [61]. In rats with self-administered cocaine, the expression of ΔFosB increased in the mPFC and orbitofrontal regions, while their performance in attention and decision-making tasks decreased [62]. During cocaine withdrawal following chronic cocaine administration, mice showed memory deficits, especially in hippocampal-dependent memory, and increased basal c-Fos expression [63]. Glutamate is a major factor promoting oxidative stress in the brain, and excessive glutamate receptor activation can induce ROS generation through cell death [58, 64]. In contrast, GABA and glutathione (GSH) inhibit nerve excitability and improve antioxidant capability [65]. In mice administered cocaine,

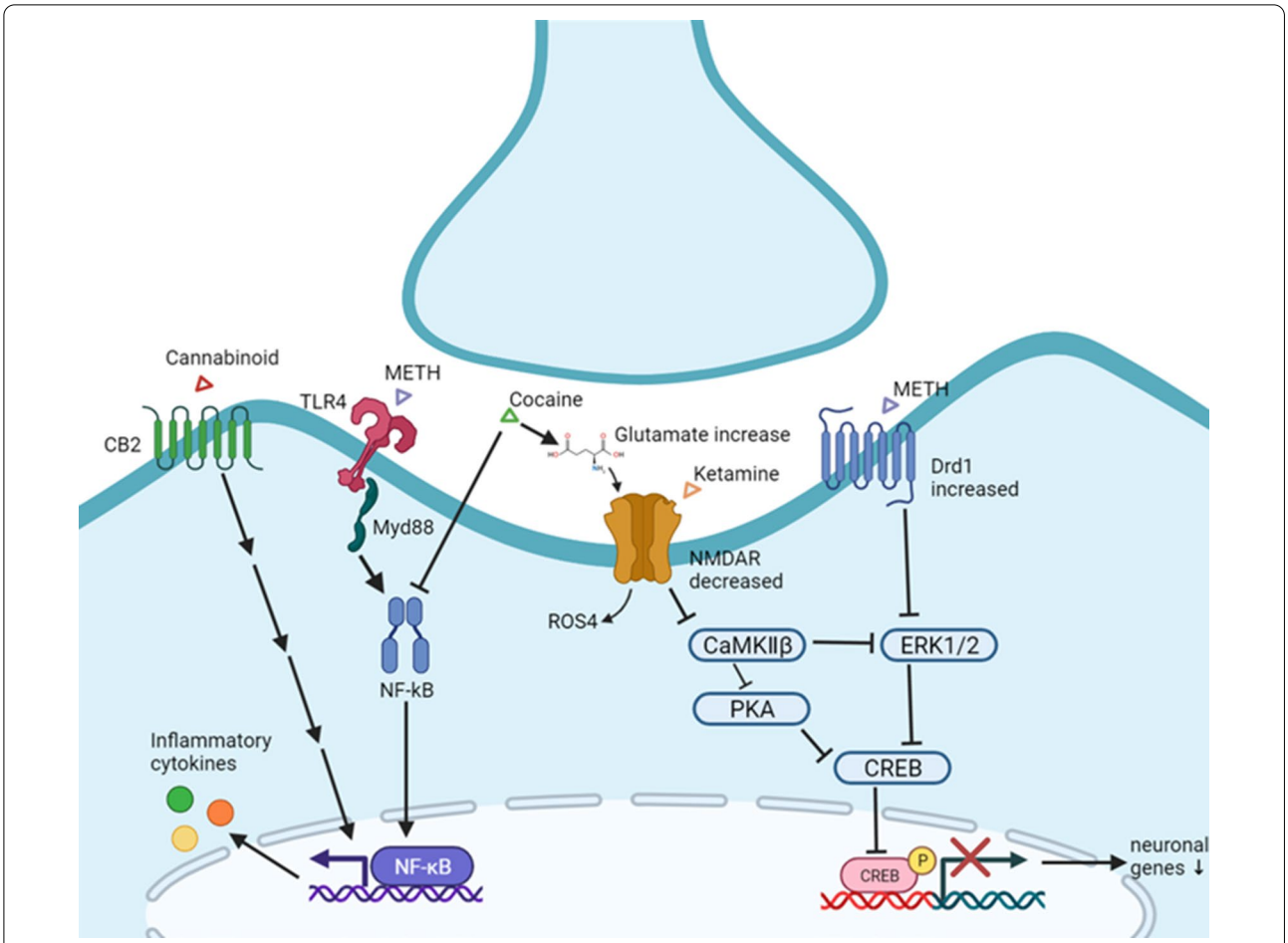

Fig. 1 Summary of the various effects of addictive drugs on cellular messenger molecules affecting cognitive impairment. METH induces inflammatory cytokines through TLR, Myd88, and NF-κB pathways. Cannabinoids induces the production of inflammatory cytokines via CB_2. In contrast, cocaine inhibits NF-κB activation. In addition, cocaine induces ROS by increasing glutamate levels. Ketamine interferes with CaMKIIβ and PKA activity as it decreases NMDAR and ultimately blocks CREB activation, thereby reducing neuronal gene transcription. Likewise, METH inhibits CREB activation by upregulating the expression of Drd1 and decreasing ERK 1/2 phosphorylation. *METH* methamphetamine, *TLR* Toll-like receptor, *NF-κB* nuclear factor kappa-B, *NMDAR* N-methyl-D-aspartate receptor, *CaMKIIβ* Ca^{2+}/calmodulin-dependent protein kinase II, *ROS* reactive oxygen species, PKA, protein kinase A, *CREB* cAMP response element-binding protein, *ERK1/2*, extracellular signal-regulated kinase 1/2, *Drd1* dopamine receptor 1

although good performance was observed in new spatial learning and memory acquisition, memory recovery was impaired. In these animals, decreased NF-κB expression in the PFC may potentially regulate the expression of genes involved in synaptic plasticity and altered cognitive function. Furthermore, both hippocampal GSH concentration and Gpx activity were reduced. The decrease in GSH levels may be related to oxidative stress by reducing neuronal inhibitory function [66]. Cortisol, a stress hormone, is induced by FosB and mediates IL8 production [67]. High cortisol levels have been detected in individuals with severe cognitive impairment [68]. The cocaine-dependent group showed low cognitive performance in verbal learning, memory, and executive ability tasks, along with a high level of salivary cortisol [69]. Thiobarbituric acid elicits oxidative stress and represents peroxidized lipids in vivo [70]. Repeated cocaine inhalation was found to impair spatial working memory and elevated striatal SOD activity, while levels of hippocampal thiobarbituric acid-reactive species were reduced [71]. These findings suggest that repeated cocaine inhalation might induce oxidative stress in the hippocampus and striatum, damaging long-term memory.

Conclusions

Determining how addictive drugs cause cognitive impairment could potentially bridge the gap between our current understanding and treatment strategies for cognitive disorders. Drug use and addiction can affect brain function and cause cognitive impairment.

Addictive drugs reportedly cause cognitive impairment by inducing neuroinflammation. These drugs increase TLR4 and MyD88 levels, thereby stimulating the production of inflammatory factors. As a result, NF-κB undergoes phosphorylation, resulting in the nuclear transcription of inflammatory cytokines. Addictive drugs can induce the overproduction of inflammatory cytokines in the brain, thereby reducing cognitive ability. We postulate that the NF-κB-induced inverted-U-shaped effects on cognitive function depend on activation. Both markedly high and low levels of NF-κB activity may reduce cognitive ability. However, further studies are required to establish conclusive results. An in-depth investigation to elucidate the mechanism of inflammatory cytokine overexpression induced by addiction drugs could provide a novel therapeutic direction for cognitive disorders.

The CREB pathway is another important mechanism underlying addictive drug-induced cognitive impairment. METH treatment increased the expression of Drd1, and elevated Drd1 expression prevented ERK 1/2 phosphorylation. Ketamine decreased NMDA receptor expression and is also related to reduced phosphorylation of CaMKIIβ, ERK 1/2, PKA, and CREB. In the absence of ERK and PKA phosphorylation, CREB does not undergo phosphorylation, and genes involved in neurogenesis are not transcribed. Dysregulation of this pathway eventually leads to cognitive impairment.

Drug abuse can seriously affect brain function through diverse pathways (Fig. 1), resulting in cognitive impairment. By understanding the effect of these distinct pathways on the brain, we can identify novel strategies for combating cognitive disorders.

Abbreviations

METH: Methamphetamine; DAT: Dopamine transporter; Drd1: Dopamine receptor 1; mPFC: Medial prefrontal cortex; Drd2: Dopamine receptor 2; NORT: Novel object recognition test; ERK1/2: Extracellular signal-regulated kinase 1/2; MAPK: Member of the mitogen-activated protein kinase; AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA: *N*-methyl-D-aspartate; IL: Interleukin; TNF: Tumor necrosis factor; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor kappa-B; BDNF: Brain-derived neurotrophic factor; CREB: CAMP response element-binding protein; PKA: Protein kinase A; CaMKIIβ: Ca^{2+}/calmodulin-dependent protein kinase II; PKCγ: Protein kinase C-gamma; IGF-II: Insulin-like growth factor II; ROS: Reactive oxygen species; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; GSH: Glutathione; CB: Cannabinoid receptor; Δ9-THC: Δ9-Tetrahydrocannabinol; Rab-1A: Ras-related protein; PGAM1: Phosphoglycerate mutase 1; Iba1: Ionized calcium-binding adapter molecule 1; COX-2: Cyclooxygenase-2; iNOS: Inducible nitric oxide synthase; AD: Alzheimer's disease.

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Authors' contributions

HS: Literature search, rough and draft revision, and approval of the manuscript. DK: Literature search, revision of draft, approval, and communication of manuscript. MK: Supervisor, the conceptualization of work, lead the discussions, interpretation of results, the authenticity of results, final revision, and approval of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

All the information in the manuscript has been referred from the included references and is available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Chemistry Life Science, Sahmyook University, Hwarangro 815, Nowongu, Seoul 01795, Republic of Korea. [2]Department of Pharmacy, Uimyung Research Institute for Neuroscience, Sahmyook University, Hwarangro 815, Nowongu, Seoul 01795, Republic of Korea.

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